Synthesis of the C-1-C28 ABCD Unit of Spongistatin 1

Supporting Information

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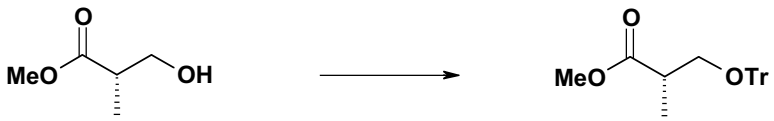
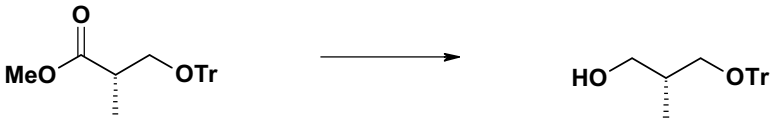
(2*S*)-Methyl –3-trityloxy-propionic acid methyl ester



To a solution of hydroxy ester (21.3 g, 0.18 mol) in CH_2Cl_2 (200 mL) was added TEA (37.7 mL, 0.27 mol), DMAP (1.1 g, 9 mmol), and trityl chloride (55.3 g, 0.19 mol). After stirring at rt for 12 h, EtOH (30 mL) was added and the reaction mixture stirred for 2 h before the reaction was quenched with saturated NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Trituration with Et_2O afforded the title compound as a colourless solid (61 g, 93%). The product was used immediately without further characterisation.

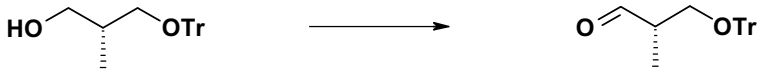
(2*R*)-Methyl-3-trityloxypropan-1-ol



To a solution of ester (36 g, 0.1 mol) in THF (360 mL) at 0 ^oC was added $LiAlH_4$ (1.0 M solution in THF, 100mL) *via* cannula over 45 min. The reaction mixture was stirred at rt for 2 h. The reaction mixture was cooled to 0 ^oC and quenched with H_2O (25 mL) followed by Rochelle's salt solution (250 mL) and the reaction mixture stirred at rt for 12 h. The aqueous layer was separated and extracted with EtOAc (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a colourless oil (32.5 g, 98%) with spectral data in good agreement with literature values[69]; R_f (Et_2O:petrol, 1:1) 0.6; $[\alpha]_D^{25}$ +24.7 (*c* 0.36, $CHCl_3$); ν_{max} (thin

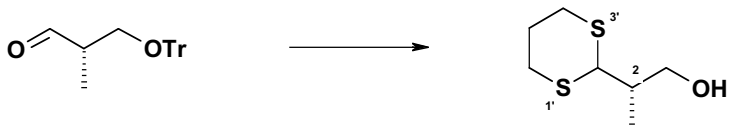
film)/cm^{-1} 3671s (OH), 2033s, 1499m, 1450m; δ_H (400 MHz; $CDCl_3$) 0.87 (3H, d, *J* 6.9, 2-CH_3), 2.24 (1H, m, 2-H), 3.04 (1H, ap. t, *J* 7.8, 3-H_A), 3.23 (1H, dd, *J* 9.1, 4.6, 3-H_B), 3.59 (2H, m, 1-H_A and 1-H_B), 7.22-7.35 (9H, m, Ar-H), 7.43-7.48 (6H, m, Ar-H).

(2*S*)-Methyl-3-trityloxyproprionaldehyde



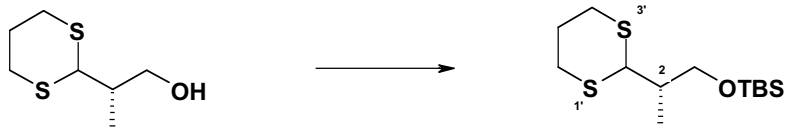
To a solution of oxalyl chloride (0.52 mL, 6 mmol) in CH_2Cl_2 (10 mL) at –78 ^oC was added DMSO (1.06 mL, 15 mmol). After stirring at this temperature for 20 min a solution of alcohol (1.00 g, 3 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred at –78 ^oC for a futher 30 min before the addition of DIPEA (2.10 mL, 12 mmol). After 15 min the reaction mixture was warmed to 0 ^oC and quenched with pH 7.0 buffer solution then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a pale yellow oil (0.96 g, 96%) with spectral data in good agreement with literature values[70]; R_f (Et_2O:petrol, 1:3) 0.58; ν_{max} (thin film)/cm^{-1} 2876w, 1721s (C=O), 1596w, 1490m; δ_H (400 MHz; $CDCl_3$) 1.12 (3H, d, *J* 7.0, 2-CH_3), 2.62 (1H, m, 2-H), 3.32-3.40 (2H, m, 3-H_A and 3-H_B), 7.24-7.32 (9H, m, Ar-H), 7.38-7.43 (6H, m, Ar-H), 9.69 (1H, d, *J* 1.6, 1-H).

(2*S*)-2-(1',3'-dithian-2'-yl)-1-propanol



To a solution of aldehyde (35.6 g, 0.107 mol) in CH_2Cl_2 (300 mL) at –78 ^{o}C was added 1,3-propanedithiol (21.65 mL, 0.215 mol) over 10 min. To the resultant solution was added $BF_3.Et_2O$ (26.5 mL, 0.215 mol) dropwise and the solution stirred at –78 ^{o}C for 30 min then warmed to rt over 3 h. The reaction was then carefully quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:2 then 1:1 then 1:0) afforded the title compound () as a yellow oil (18.4 g, 95%) with spectral data in good agreement with literature values[71]; R_f (Et_2O:petrol, 1:2) 0.20; $[\alpha]_D^{25}$ +8.0 (*c* 0.97, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3391br (OH), 2898m, 1456w, 1034s (C-O); δ_H (400 MHz; $CDCl_3$) 1.08 (3H, d, *J* 7.0, 2-CH_3), 1.80-1.90 (1H, m, 2-H), 2.04-2.11 (3H, m, 5'-H_A, 5'-H_B and 1-OH), 2.81-2.94 (4H, m, 4'-H_A, 4'-H_B, 6'-H_A and 6'-H_B), 3.66 (2H, m, 1-H_A and 1-H_B), 4.28 (1H, d, J 4.9, 2'-H).

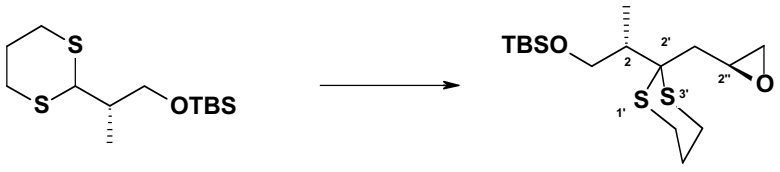
(2*S*)-1-(*tert*-Butyldimethylsiloxy)-2-(1',3'-dithian-2'-yl)-1-propane (11)



11

To a solution of alcohol (18.2 g, 102 mmol) in THF (100 mL) was added imidazole (13.9 g, 204 mmol) and TBSCl (23.08 g, 153 mmol) and the resultant mixture stirred for 2 h at rt, then diluted with EtOAc (50 mL) and partitioned with saturated NH_4Cl solution (50 mL). The aqueous phase was separated and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (0:100 then gradient to 5:95) afforded the title compound () as a colourless oil (22.6 g, 76%); R_f (Et_2O:petrol, 1:2) 0.75; $[\alpha]_D^{25}$ -1.0; (*c* 1.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2953w, 2856w, 1470w, 1249m, 833s (Si-O); δ_H (400 MHz; $CDCl_3$) 0.05 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.06 (3H, d, *J* 6.9, 2-CH_3), 1.79-1.90 (1H, m, 2-H), 2.02-2.11 (2H, m, 5'-H_A and 5'-H_B), 2.86-2.92 (4H, m, 4'-H_A, 4'-H_B, 6'-H_A and 6'-H_B), 3.54 (1H, dd, *J* 6.2, 3.8, 1-H_A), 3.68 (1H, dd, *J* 6.9, 3.1, 1-H_B), 4.30 (1H, d, *J* 4.7, 2'-H); δ_C (100 MHz; $CDCl_3$) –5.4 ($Si(CH_3)_2$), 13.7 (2-CCH_3), 18.3 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 26.4 (5'-C), 30.6 and 31.2 (4'-C and 6'-C), 41.1 (2-C), 51.6 (2'-C), 64.9 (1-C). Found (+ESI): $(MNa)^+$ 315.1249. $C_{13}H_{28}OS_2SiNa$ requires 315.1249.

(2*S*)-*tert*-Butyldimethyl-[2-(2''-oxyranylmethyl)-1',3'-dithian-2'-yl]-propoxysilane (148)

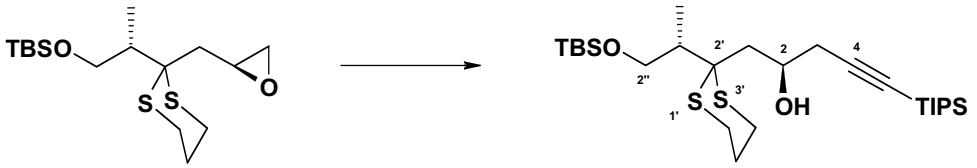


11

To a solution of dithiane **11** (2.87 g, 9.8 mmol) in THF (50 mL) was added ^{n}BuLi (1.6 M solution in hexanes, 12.28 mL, 19.6 mmol) slowly at rt. The reaction mixture was stirred for 10 min then cooled to –10 ^oC before (*S*)-(-)-epichlorohydrin (1.00 g, 10.7 mmol, 1.1 eq) was added and resultant solution stirred overnight at rt. The reaction was quenched with saturated NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 100 mL). The

combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:8 then 1:5 then 1:3) yielded the title compound (2.78 g, 81%) as a colourless oil; R_f (Et_2O:petrol, 1:3) 0.43; $[\alpha]_D^{25}$ -23.8; (*c* 0.31, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2927s, 2856m, 1471w, 1086s (Si-O); δ_H (600 MHz; $CDCl_3$) 0.06 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.20 (3H, d, *J* 6.9, 2-CH_3), 1.95 (2H, m, 5'-H_A and 5'-H_B), 2.13-2.24 (2H, ap. dq, *J* 15.2, 5.7, 1''-H_A and 1''-H_B), 2.30 (1H, m, 2-H), 2.53 (1H, dd, *J* 4.9, 2.7, 3''-H_A), 2.78-2.84 (5H, m, 4'-H_A, 4'-H_B, 6'-H_A, 6'-H_B and 3''-H_B), 3.25 (1H, ap. ddt, *J* 6.4, 3.4, 2''-H), 3.60 (1H, dd, *J* 9.8, 8.0, 1-H_A), 4.08 (1H, dd, *J* 9.9, 3.6, 1-H_B); δ_C (100 MHz; $CDCl_3$) –5.3 ($Si(CH_3)_2$) 12.7 (2-C*C*H_3), 18.2 (Si*C*$(CH_3)_3$), 24.9 (5'-C), 25.8, 26.0 (4'-C and 6'-C), 25.9 ($SiC(CH_3)_3$), 39.2 (1''-C), 42.3 (1-C), 47.2 (3''-C), 49.3 (2''-C), 55.6 (2'-C), 64.8 (2-C); Found (+ESI): $(MNa)^+$ 371.1519. $C_{16}H_{32}O_2S_2SiNa$ requires 371.1511.

(2*R*,1''*S*)-1-{2'-[2''(*tert*-Butyldimethylsilanyloxy)-1''-methylethyl]-[1',3']-dithian-2'-yl}-5-triisopropylsilanyl-pent-4-yn-2-ol (12)

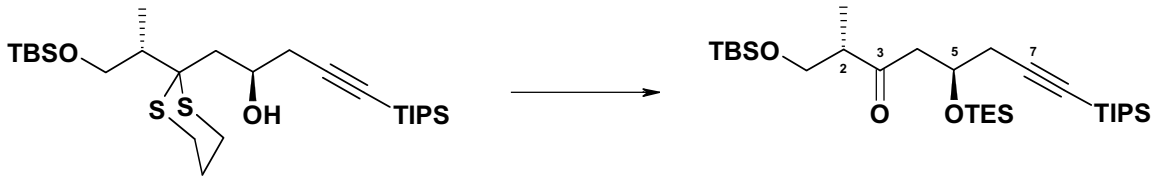


12

To a solution of triisopropylsilylacetylene (2.65 mL, 11.8 mmol) in THF (75 mL) at –78 °C was added ^{n}BuLi (1.6 M solution in hexanes, 11.0 mmol, 6.90 mL). After 1 h BF_3.THF (1.22 mL, 11.0 mmol) was added to the reaction mixture and stirred at –78 °C for a further 1 h. To this resultant solution was added a solution of epoxide (2.75 g, 7.89 mmol) in THF (25 mL) and reaction stirred for 1 h. The reaction was quenched with the addition of saturated NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:10 then

1:6) afforded the title compound as a colourless oil (3.66 g, 87%); R_f (Et_2O:petrol, 1:9) 0.21; $[\alpha]_D^{25}$ -19.7; (*c* 1.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2937s, 2864s, 2166w (C≡C), 1463 m; δ_H (400 MHz; $CDCl_3$) 0.05 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.05 (21H, m, $Si(CH(CH_3)_2)_3$ and $Si(CH(CH_3)_2)_3$), 1.21 (3H, d, *J* 6.8, 1"-CH_3), 1.95 (2H, m, 5'-H_A and 5'-H_B), 2.20 (2H, dd, *J* 6.3, 1.8, 1-H_A and 1-H_B), 2.38 (1H, m, 1"-H), 2.50 (2H, dd, *J* 6.5, 5.5, 3-H_A and 3-H_B), 2.88 (4H, m, 4'-H_A, 4'-H_B, 6'-H_A and 6'-H_B), 3.23 (1H, d, *J* 2.9, OH), 3.52 (1H, dd, *J* 9.6, 8.3, 2"-H_A), 4.04 (1H, dd, *J* 9.8, 3.6, 2"-H_B), 4.24 (1H, m, 2-H); δ_C (100 MHz; $CDCl_3$) -5.3 (2x $SiCH_3$), 11.3 ($Si(CH(CH_3)_2)_3$), 13.1 (1"-CCH_3), 18.3 ($SiC(CH_3)_3$), 18.6 ($Si(CH(CH_3)_2)_3$), 24.8 (5'-C), 25.9 ($SiC(CH_3)_3$), 25.9 (4'-C and 6'-C), 29.3 (3-C), 41.4 (1-C), 42.3 (1"-C), 55.8 (2'-C), 64.7 (2"-C), 67.3 (2-C), 83.1 (5-C), 104.8 (4-C); Found (+ESI): $(MNa)^+$ 553.3019. $C_{27}H_{54}O_2S_2Si_2Na$ requires 553.3002.

(2*S*,5*R*)-1-(*tert*-Butyldimethylsilanoxy)-2-methyl-5-triethylsilanoxy-8-triisopropylsilanyl-oct-7-yn-3-one (13)

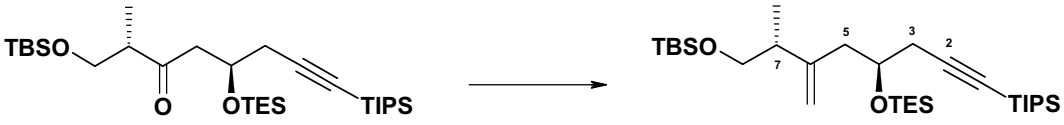


12 **13**

Dithiane **12** (3.64 g, 6.86 mmol) was dissolved in MeCN (80 mL) and saturated $NaHCO_3$ solution (40 mL) then cooled to 0 ^oC, whereupon iodine (6.97 g, 27.4 mmol) was added portionwise over 15 min. The reaction mixture was then allowed to warmed to rt over 1 h before quenching with a 1:1 solution of saturated $NaHCO_3$ and $Na_2S_2O_3$ (100 mL). The aqueous phase was separated and extracted with Et_2O (4 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford crude hydroxy ketone. The crude material was dissolved in THF (100 mL) and imidazole (1.87 g, 27.4 mmol) and TESCl (3.45 mL, 20.5 mmol) added

sequentially. The reaction mixture was stirred at rt for 1 h before quenching with saturated NH_4Cl solution (50 mL). The aqueous phase was separated and extracted with Et_2O (4 x 150 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:hexane (1:25) afforded the title compound () as a pale yellow oil (3.61 g, 95%, over 2 steps); R_f (Et_2O:hexane, 1:25) 0.36; $[\alpha]_D^{25}$ -7.4; (*c* 1.9, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954s, 2875s, 2174w (C≡C), 1716s (C=O), 1462s; δ_H (400 MHz; $CDCl_3$) 0.02 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.52 (6H, q, *J* 7.9, $Si(CH_2CH_3)_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.93 (9H, t, *J* 5.7, $Si(CH_2CH_3)_3$), 1.05 (24H, m, $Si(CH(CH_3)_2)_3$, $Si(CH(CH_3)_2)_3$ and 2-CH_3), 2.46 (2H, ap. d, *J* 5.2, 6-H_A and 6-H_B), 2.71 (1H, m, 2-H), 2.78 (1H, ap. d, *J* 6.7, 4-H_A), 2.90 (1H, dd, *J* 11.6, 5.4, 4-H_B), 3.56 (1H, dd, *J* 9.9, 6.2, 1-H_A), 3.77 (1H, dd, *J* 9.9, 6.7, 1-H_B), 4.31 (1H, m, 5-H); δ_C (100 MHz; $CDCl_3$) -5.6 (2x $SiCH_3$), 4.9 ($Si(CH_2CH_3)_3$), 6.8 ($Si(CH_2CH_3)_3$), 11.3 ($Si(CH(CH_3)_2)_3$), 12.8 (2-CH_3), 18.2 ($SiC(CH_3)_3$), 18.6 ($Si(CH(CH_3)_2)_3$), 25.8 ($SiC(CH_3)_3$), 28.7 (6-C), 48.5 (4-C), 49.6 (2-C), 64.9 (1-C), 66.6 (5-C), 82.8 (8-C), 104.9 (7-C), 211.6 (3-C); Found (+ESI): $(MNa)^+$ 577.3884. $C_{30}H_{62}O_3Si_3Na$ requires 577.3905.

(4*S*,7*R*)-8-(*tert*-Butyldimethylsilanoxy)-7-methyl-6-methylene-4-triethylsilanyloxy-1-triisopropylsilanyl-oct-1-yne (14)



13 **14**

To a Smith microwave vial containing ketone **13** (200 mg, 0.3 mmol) and ionic liquid, 1-ethyl-3-methyl-imidazolium hexafluorophosphate (Aldrich, 40 mg), was added the Petasis reagent (4.5 mL of 0.15 M solution in toluene, 0.6 mmol, 2 eq). The vial was transferred immediately to a Personal Chemistry Emrys Liberator Microwave[72] and microwaved for 10 min at 160 ^oC. The reaction mixture was concentrated *in vacuo* and

flash column chromatography on residue, eluting with Et_2O:petrol (1:100) afforded the title compound as a colourless oil (166 mg, 83%); R_f(Et_2O:petrol, 1:100) 0.14; $[\alpha]_D^{25}$ -2.6; (*c* 1.35, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955s, 2865m, 2172w (C≡C), 1640 (C=C), 1463m; δ_H (400 MHz; $CDCl_3$) 0.03 (6H, s, $Si(CH_3)_2$), 0.60 (6H, q, *J* 7.8, $Si(CH_2CH_3)_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.96 (9H, t, *J* 8.0, $Si(CH_2CH_3)_3$), 1.07 (24H, m, $Si(CH(CH_3)_2)_3$, $Si(CH(CH_3)_2)_3$ and 7-CH_3), 2.28 (2H, m, 7-H and 5-H_A), 3.36 (1H, dd, *J* 9.6, 7.6, 8-H_A), 3.41 (3H, m, 3-H_A, 3-H_B and 5-H_B), 3.61 (1H, dd, *J*, 9.5, 5.3, 8-H_B), 3.93 (1H, m, 4-H), 4.84 (1H, s, 6-CH_AH_B), 4.90 (1H, s, 6-CH_AH_B); δ_C (100 MHz; $CDCl_3$) -5.0 $(SiCH_3)_2$, 5.4 $(Si(CH_2CH_3)_3)$, 7.3 $(Si(CH_2CH_3)_3)$, 11.8 $(Si(CH(CH_3)_2)_3)$, 17.0 (7-CH_3), 18.7 $(SiC(CH_3)_3)$, 19.0 $(Si(CH(CH_3)_2)_3)$, 26.3 $(SiC(CH_3)_3)$, 28.9 (3-C), 42.4 (7-C), 43.2 (5-C), 67.8 (8-C), 70.6 (4-C), 82.6 (1-C), 106.2 (2-C), 112.2 (6-CH_2), 148.8 (6-C); Found (+ESI): $(MNa)^+$ 575.4120. $C_{31}H_{64}O_2Si_3Na$ requires 575.4112.

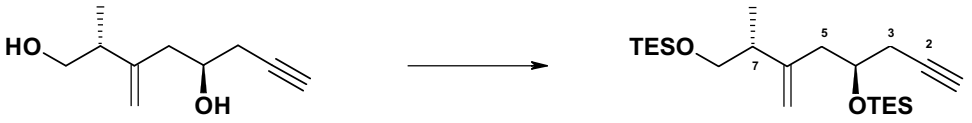
(2*R*, 5*R*)-2-Methyl-3-methyleneoct-7-yne-1,5-diol

14

To a solution of alkene (188 mg, 0.3 mmol) in THF (5 mL) at rt was added TBAF (1 M solution in THF, 1.5 mL, 1.5 mmol). After 2 h the reaction was diluted with Et_2O (30 mL) and quenched with saturated NH_4Cl (50 mL). The aqueous layer was separated and extracted with Et_2O (5 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (2:1 then 4:1) afforded the title compound as a yellow oil (48 mg, 84%); R_f(Et_2O) 0.29; $[\alpha]_D^{25}$ +7.0; (*c* 1.2, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3295br (OH), 2929s, 2346w, 2120w (C≡C), 1642m (C=C); δ_H (600 MHz; $CDCl_3$) 1.07 (3H, d, *J* 7.0, 2-CH_3), 1.60-1.75 (2H, bs, 1-OH and 5-OH), 2.07 (1H, t, *J* 2.6, 8-H), 2.21 (1H, dd, *J* 14.3, 9.1, 2-H), 2.42 (4H, m, 4-H_A, 4-H_B, 6-H_A and 6-H_B), 3.59 (2H, m, 1-H_A and 1-H_B), 3.96

(1H, m, 5-H), 5.04 (2H, d, *J* 6.1, 3-CH_2); δ_C (150 MHz; $CDCl_3$) 16.4 (2-CH_3), 27.0 (6-C), 41.9 (4-C), 42.1 (2-C), 66.3 (1-C), 68.7 (5-C), 70.9 (8-C), 80.6 (7-C), 113.4 (3-CH_2), 148.0 (3-C); Found (+ESI): $(MNa)^+$ 191.1042. $C_{10}H_{16}O_2Na$ requires 191.1048.

(4*R*, 7*R*)-7-Methyl-6-methylene-4,8-bis(triethylsilanyloxy)-oct-1-yne (8)



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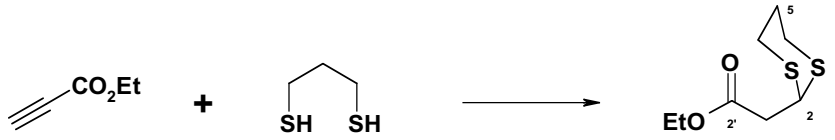
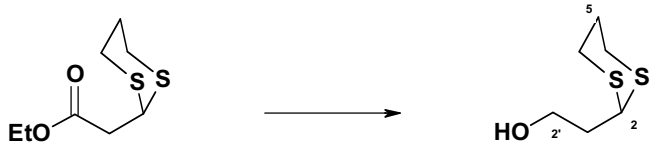
To a solution of diol (1.39 g, 8.26 mmol) in THF (40 mL) at rt was added imidazole (2.25 g, 33 mmol) and TESCl (4.2 mL, 24.8 mmol). The reaction was quenched after 45 min with saturated NH_4Cl solution and extracted with EtOAc (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:100 then 3:100) afforded the title compound () as a pale yellow oil (2.8 g, 85%); R_f (Et_2O:petrol, 1:100) 0.15; $[\alpha]_D^{25}$ +6.6; (*c* 2.3, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3314w, 2954s, 2911s, 2876s, 1642w (C=C); δ_H (600 MHz; $CDCl_3$) 0.59 (6H, q, *J* 8.0, Si(C*H*$_2$CH$_3$)$_3$), 0.61 (6H, q, *J* 9.4 Si(C*H*$_2$CH$_3$)$_3$), 0.96 (9H, t, *J* 8.0, Si(CH$_2$C*H*$_3$)$_3$), 0.97 (9H, t, *J* 8.0, Si(CH$_2$C*H*$_3$)$_3$), 1.06 (3H, d, *J* 6.8, 7-CH_3), 1.98 (1H, t, *J* 2.6, 1-H), 2.20-2.40 (5H, m, 5-H_A, 5-H_B, 3-H_A, 3-H_B and 7-H), 3.37 (1H, dd, *J* 9.7, 7.8, 8-H_A), 3.64 (1H, dd, *J* 8.7, 5.4, 8-H_B), 3.95 (1H, m, 4-H), 4.87 (2H, d, *J* 11.7, 6-C*H*$_A$*H*$_B$); δ_C (150 MHz; $CDCl_3$) 4.4 (Si(*C*H$_2$CH$_3$)$_3$), 4.9 (Si(*C*H$_2$CH$_3$)$_3$), 6.7 (Si(CH$_2$*C*H$_3$)$_3$), 6.8 (Si(CH$_2$*C*H$_3$)$_3$), 16.6 (7-CH_3) 27.0 (3-C), 42.0 (5-C), 43.2 (7-C), 67.3 (8-C), 69.8 (4-C), 70.0 (1-C), 81.7 (2-C), 111.9 (6-CH_2), 148.3 (6-C); Found (+ESI): $(MNa)^+$ 419.2794. $C_{22}H_{44}O_2Si_2Na$ requires 419.2778.

(1,3)-Dithianyl-2-yl ethanoic acid ethyl ester



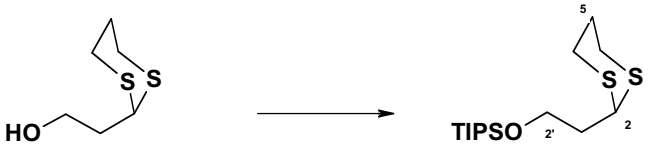
Sodium ethoxide (10.0 g, 145 mmol) was added in one portion to a stirred solution of ethyl propiolate (10.6 g, 108 mmol) and 1,3-propanedithiol (11.75 g, 108 mmol) in THF:EtOH (2:1) (180 mL) at –10 ^{o}C (ice/acetone bath). The resulting solution was stirred for 14 h, allowing the temperature to rise to 0 °C. After this time, the mixture was quenched with saturated NH_4Cl solution (100 mL). The aqueous layer was separated and extracted with Et_2O (4 x 100 mL). The combined organic extracts were washed with saturated NH_4Cl solution (100 mL), saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Flash chromatography on silica gel (Petrol-Et_2O, 19:1 then 9:1 then 4:1) afforded the title compound (11.55 g, 52%) as a pale yellow oil; R_f (Et_2O:Petrol, 3:7) 0.29; ν_{max} (thin film)/cm^{-1} 2981w (C-H stretch), 2901w (C-H stretch), 1731s (C=O), 1422s (C-H deformation); δ_H (400 MHz; $CDCl_3$) 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 1.87-1.94 (1H, m, 5-H_A), 2.05-2.13 (1H, m, 5-H_B), 2.16 (2H, d, *J* 7.4, 1'-H_A and 1'-H_B), 2.84-2.93 (4H, m, 4-H_A, 4-H_B, 6-H_A, 6-H_B), 4.18 (2H, q, *J* 7.1, OCH_2CH_3), 4.40 (1H, t, *J* 7.4, 2-H); δ_C (100 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 25.3 (5-C), 29.5 (4-C, 6-C), 40.6 (1'-C), 41.9 (2-C), 61.0 (OCH_2CH_3), 169.7 (2'-C); Found (+EI): $(M)^+$, 206.0436. $C_8H_{14}O_2S_2$ requires 206.0435.

1,3-Dithian-2-yl ethanol



To solid $LiAlH_4$ (2.11 g, 54.4 mmol) cooled at –78 °C was added THF (120 mL) dropwise (careful : strong exotherm). After stirring of the resulting suspension for 15 min a solution of the ester (11.53 g, 55.9 mmol) in THF (50 mL) was added dropwise. The reaction mixture was then stirred at –78 °C for 3 h and for a further 18 h at rt. The reaction mixture was then quenched by the slow addition of water (8 mL) at 0 °C followed by aqueous Rochelle's salt (200 mL), the mixture was stirred at rt for 20 h. The aqueous layer was separated and extracted with Et_2O (2 x 300 mL). The combined organic extracts were washed with distilled water (300 mL) and brine (300 mL), dried ($MgSO_4$). The solution was then filtered through a small pad of silica gel (Et_2O) and concentrated *in vacuo* afforded the title compound (9.1 g, 99%) as a pale yellow oil; R_f (Et_2O:Petrol, 3:7) 0.11; ν_{max} (thin film)/cm^{-1} 3392br (OH), 2932w (C-H stretch), 2899w (C-H stretch), 1422s (C-H deformation); δ_H (400 MHz; $CDCl_3$) 1.73 (1H, t, *J* 5.4, OH), 1.84-1.95 (1H, m, 5-H_A), 2.03 (2H, ap.dd (dt), *J* 7.0, 6.0, 1'-H_A and 1'-H_B), 2.08-2.16 (1H, m, 5-H_B), 2.81-2.92 (4H, m, 4-H_A, 4-H_B, 6-H_A, 6-H_B), 3.83 (2H, ap.dd (dt), *J*, 11.0, 6.0, 2'-H_A and 2'-H_B), 4.23 (1H, t, *J* 7.0, 2-H); δ_C (100 MHz; $CDCl_3$) 25.9 (5-C), 30.3 (4-C, 6-C), 38.0 (1'-C), 44.4 (2-C), 59.8 (2'-C); Found (+EI): $(M)^+$, 164.0330. $C_6H_{12}OS_2$ requires 164.0335.

(1,3)-Dithian-2-yl-(ethoxy)trisopropylsilane (15)

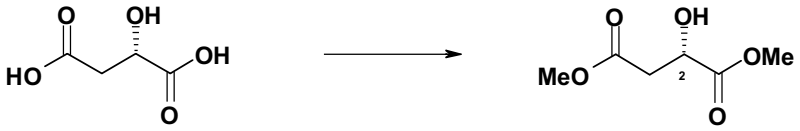


15

A solution of alcohol (9.10 g, 55.4 mmol) in THF (50 mL) was added to a stirred solution of imidazole (9.42 g, 138 mmol) and triisopropylsilylchloride (17.8 mL, 83 mmol) in THF (50 mL) cooled to 0 °C. The resulting solution was allowed to warm to rt and stirred for a further 16 h. After this time, water (150 mL) was added and the mixture stirred

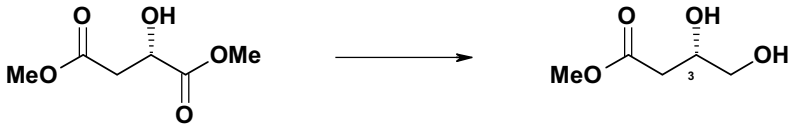
vigorously for 0.5 h. The aqueous layer was separated and extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (Et_2O:petrol, 19:1 then 9:1 then 4:1) afforded the title compound () (17.20 g, 97%) as a pale yellow oil; R_f (Petrol-Et_2O, 1:1) 0.70; ν_{max} (thin film)/cm^{-1} 2941w (C-H stretch), 2895w (C-H stretch), 2865 (C-H stretch), 1463s (C-H deformation); δ_H (400 MHz; $CDCl_3$) 1.01-1.14, (21H, m, (Si-C*H*(CH_3)$_2$), 1.83-1.93 (1H, m, 5-H_A), 1.98 (2H, ap.dd (dt), *J* 8.1, 1.4, (1'-H_A and 1'-H_B), 2.08-2.13 (1H, m, 5-H_B), 2.80-2.90 (4H, m, 4-H_A, 4-H_B, 6-H_A, 6-H_B), 3.85 (2H, t, *J* 6.3, 2'-H_A and 2'-H_B), 4.25 (1H, t, *J* 7.0, 2-H); δ_C (100 MHz; $CDCl_3$) 12.0 (Si-*C*H(CH_3)$_2$), 18.0 (Si-CH(*C*H_3)$_2$), 26.1 (5-C), 30.2 (4-C, 6-C), 38.6 (1'-C), 43.8 (2-C), 59.7 (2'-C); Found (+EI): $(M)^+$, 320.1650. $C_{15}H_{32}OS_2$ requires 320.1664.

(2*S*)-2-Hydroxysuccinic acid dimethyl ester



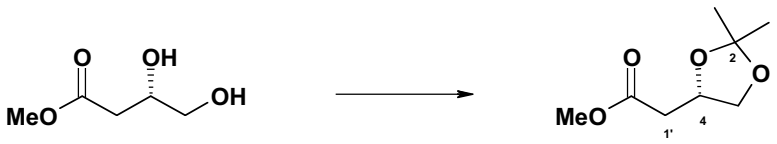
To MeOH (300 mL) was added acetyl chloride (15.5 mL) dropwise. The resultant solution was stirred for 10 min, then (*S*)-malic acid (47.0 g, 0.35 mol) was added and the reaction mixture stirred at rt for 18 h. The reaction mixture was concentrated *in vacuo.* Flash column chromatography eluting with CH_2Cl_2:MeOH (95:5) afforded the title compound as a pale yellow oil (51.4 g, 90%) with spectral data in good agreement with literature values[73]; R_f (CH_2Cl_2:MeOH, 95:5) 0.51; $[\alpha]_D^{25}$ +3.1; (*c* 0.8, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3482br (OH), 2958w, 1731s (C=O), 1438s; δ_H (400 MHz; $CDCl_3$) 2.76-2.90 (2H, dd, *J* 16.4, 4.4, 3-H_A and 3-H_B), 3.20 (1H, bs, OH), 3.72 (3H, s, 1-CO_2CH_3), 3.81 (3H, s, 4-CO_2CH_3), 4.49-4.52 (1H, dd, *J* 5.9, 4.6, 2-H)

(3*S*)-3,4-Dihydroxybutyric acid methyl ester



To a solution of starting diester (50.0 g, 0.3 mol) in THF (300 mL) at rt was added $BH_3.Me_2S$ solution (10 M solution in THF, 30 mL, 0.3 mol). After 1 h, $NaBH_4$ (500 mg) was added and stirring continued for a further 45 min. After this time MeOH (100 mL) was added and the reaction mixture was stirred for 30 min. The reaction was quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with EtOAc (3 x 150 mL). Combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with EtOAc afforded the title compound as a colourless oil (35.1 g, 85%) with spectral data in good agreement with literature values[74]; R_f (EtOAc) 0.34; $[\alpha]_D^{25}$ -56.0; (*c* 0.4, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3380br (OH), 2955m, 1729s (C=O), 1439s; δ_H (400 MHz; $CDCl_3$) 2.18 (1H, t, *J* 6.1, 4-OH), 2.54 (2H, dd, *J* 16.4, 8.4, 2-H_A and 2-H_B) 3.22 (1H, d, *J* 3.9, 3-OH), 3.53 (1H, m, 4-H_A), 3.66-3.72 (1H, m, 4-H_B) overlapping with 3.72 (3H, s, CO_2CH_3), 4.13 (1H, m, 3-H).

(4*S*)-(2,2-Dimethyl-[1,3]-dioxolan-4-yl) acetic acid methyl ester



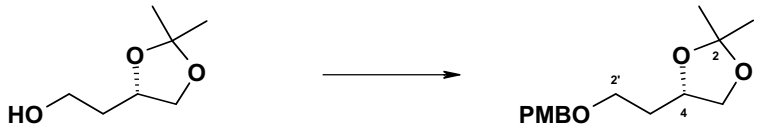
To a stirring solution of starting diol (1.0 g, 7.45 mmol) in acetone (10 mL)/2,2-dimethoxypropane (2 mL) at 0 °C was added $TsOH.H_2O$ (140 mg, 0.75 mmol). The reaction mixture was stirred for 1 h. The reaction was quenched by the addition of

saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (4 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:1) afforded the title compound as a colourless oil (1.2 g, 93%) with spectral data in good agreement with literature values[74]; R_f (Et_2O:petrol, 1:1) 0.36; $[\alpha]_D^{25}$ +9.0; (*c* 0.2, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3380br (OH), 2989m, 2362w, 1733s (C=O), 1439m; δ_H (400 MHz; $CDCl_3$) 1.37 (3H, s, 2-CH_3), 1.41 (3H, s, 2-CH_3), 2.52 (1H, dd, *J* 15.9, 7.1, 1'-H_A), 2.71 (1H, dd, *J* 15.8, 6.8, 1'-H_B), 3.65 (1H, dd, *J* 8.3, 6.4, 5-H_A), 3.70 (3H, s, CO_2CH_3), 4.15 (1H, dd, *J* 8.3, 6.0, 5-H_B), 4.47 (1H, m, 4-H).

(4*S*)-2'-(2,2-Dimethyl-[1,3]-dioxolan-4-yl)ethanol

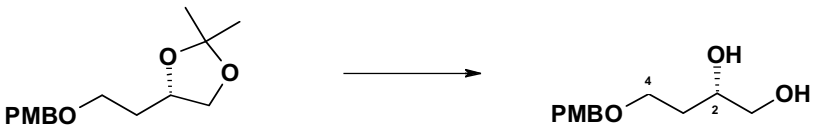
To a solution of ester (12.68 g, 72.8 mmol) in THF (100 mL) at 0 °C was added $LiAlH_4$ (72.8 mL, 1.0 M solution in THF) and the reaction mixture was stirred for 2 h. After this time the reaction mixture was quenched by careful addition of H_2O (20 mL) followed by a saturated solution of Rochelle's salt (150 mL) and stirred overnight. The layers were separated and the aqueous phase extracted with EtOAc (2 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O: petrol (1:1) afforded the title compound as a colourless oil (10.27 g, 96%) with spectral data in good agreement with literature values[74]; R_f (Et_2O:petrol, 1:2) 0.09; $[\alpha]_D^{25}$ -4.9; (*c* 0.33, MeOH); ν_{max} (thin film)/cm^{-1} 3408br (OH), 2984m, 1371s; δ_H (400 MHz; $CDCl_3$); 1.36 (3H, s, 2-CH_3), 1.42 (3H, s, 2-CH_3), 1.77-1.82 (2H, m, 1'-H_A and 1'-H_B), 2.32 (1H, t, *J* 4.7, 2'-OH), 3.58 (1H, ap. t, *J* 7.7, 5-H_A), 3.79 (2H, m, 2'-H_A and 2'-H_B), 4.08 (1H, dd, *J* 7.7, 6.0, 5-H_B) 4.26 (1H, ap. ddt, *J* 7.7, 6.3, 5.7, 4-H).

4(*S*)-[2'-(*p*-Methoxybenzyloxy)ethyl]-2,2-dimethyl-[1,3]-dioxolane



To a solution of alcohol (10.25 g, 70 mmol) in THF (25 mL) and DMF (25 mL) at rt was added NaH (60% dispersion, 4.21 g, 0.105 mol). The reaction mixture was stirred for 30 min before the addition of PMBCl (14.25 mL, 0.105 mol) followed by TBAI (1.3 g, 3.5 mmol) and the reaction mixture was stirred for a further 12 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:6 then 1:3) afforded the title compound as a yellow oil (17.5 g, 94%) with spectral data in good agreement with literature values[75]; R_f (Et_2O:petrol, 1:4) 0.18; $[\alpha]_D^{25}$ -8.4; (*c* 0.8, MeOH); ν_{max} (thin film)/cm^{-1} 2984m, 2865m, 1612m (Ar C=C), 1513s (Ar C=C) δ_H (400 MHz; $CDCl_3$) 1.35 (3H, s, 2-CH_3), 1.40 (3H, s, 2-CH_3), 1.79-1.96 (2H, m, 1'-H_A and 1'-H_B), 3.50-3.59 (3H, m, 2'-H_A, 2'-H_B and 5-H_A), 3.80 (3H, s, $ArOCH_3$), 4.05 (1H, dd, *J* 8.0, 6.0, 5-H_B), 4.20 (1H, ap. ddt, *J* 8.0, 6.3, 5.7, 4-H), 4.43 (2H, s, OCH_2Ar), 6.87 (2H, d, *J* 8.6, Ar-*meta*-H), 7.24 (2H, d, *J* 8.6, Ar-*ortho*-H).

2(*S*)-4-(*p*-Methoxybenzyloxy)-butane-1,2-diol



To a solution of acetonide (17.5 g, 65.7 mmol) in MeOH (50 mL) at rt was added TsOH.H_2O (3.75 g, 19.5 mmol). The reaction mixture was stirred for 18 h then quenched with saturated NH_4Cl (30 mL) solution and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O: petrol (1:1 then 1:0) afforded the title compound as a pale yellow oil (7.0 g, 47% conversion, based on recovered starting material (7.0 g) yield 78%); R_f (Et_2O) 0.15; $[\alpha]_D^{25}$ +4.4; (*c* 0.8, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3373br (OH), 2932m, 2863m, 1612m (Ar C=C), 1586w (Ar C=C), 1512s (Ar C=C); δ_H (400 MHz; $CDCl_3$) 1.70-1.87 (2H, m, 3-H_A and 3-H_B), 2.31 (1H, t, *J* 6.0, 1-OH), 3.11 (1H, d, *J* 3.3, 2-OH), 3.48-3.52 (1H, m, 1-H_A), 3.60-3.70 (3H, m, 1-H_B, 4-H_A and, 4-H_B), 3.80 (3H, s, $ArOCH_3$), 3.90 (1H, m, 2-H), 4.45 (2H, s, OCH_2Ar), 6.88 (2H, d, *J* 8.6, Ar-*meta*-H), 7.24 (2H, d, *J* 8.6, Ar-*ortho*-H).

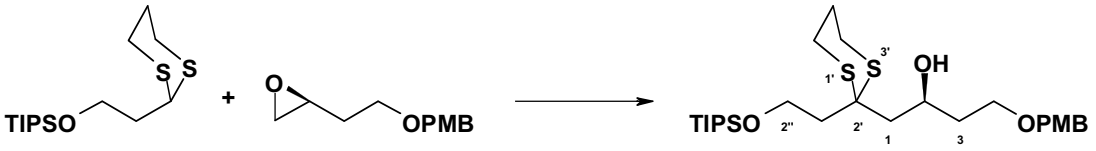
(2*S*)-2-[2'-(*p*-Methoxybenzyloxy)ethyl]-oxirane (16)

16

A solution of diol (11.68 g, 51.6 mmol) in THF (200 mL) was added to a suspension of NaH (60% dispersion, 5.16 g, 0.129 mol) in DMF (50 mL) at 0 ^oC and stirred for 30 min. To the resultant mixture was added triisopropylbenzylsulfonyl imidazole (19 g, 56.8

mmol) and the solution was stirred at rt overnight. The reaction was quenched with saturated NH_4Cl solution and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:3 then 1:1) afforded the title compound as a colourless oil (5.74 g, 53%) with spectral data in good agreement with literature values[76]; R_f (Et_2O:petrol, 1:1) 0.48; $[\alpha]_D^{25}$ -13.1; (*c* 0.58, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2924w, 2862w, 1612m (Ar C=C), 1586w (Ar C=C), 1512s (Ar C=C) ;δ_H (400 MHz; $CDCl_3$) 1.76 (1H, m, 1-H_A), 1.88 (1H, m, 1-H_B), 2.50 (1H, ap. dd, *J* 5.0, 2.7, 1'-H_A), 2.75 (1H, ap. dd, *J* 5.0, 4.4, 1'-H_B), 3.04 (1H, m, 2-H), 3.58 (2H, m, 2'-H_A and 2'-H_B) 3.79 (3H, s, $ArOCH_3$), 4.45 (2H, s, OCH_2Ar), 6.86 (2H, d, *J* 8.7, Ar-*meta*-H), 7.24 (2H, d, *J* 8.7, Ar-*ortho*-H); δ_C (100 MHz; $CDCl_3$) 32.9 (1'-C), 47.0 (1-C), 50.0 (2-C), 55.2 ($ArOCH_3$), 66.7 (2'-C), 72.7 (OCH_2Ar), 113.8 (Ar-*meta*-C), 129.2 (Ar-*ortho*-H), 130.4 (Ar-*ipso*-C) and 159.2 (Ar-*para*-C).

(2*S*)-4-(*p*-Methoxybenzyloxy)-1-[2'-(2''-triisopropylsilanoxy-ethyl)-[1',3']-dithian-2'-yl]-butan-2-ol (17)

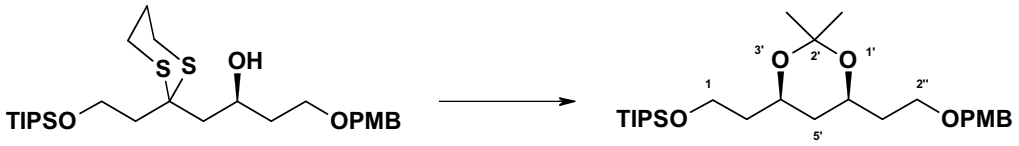


15 **16** **17**

To a stirring solution of dithiane () (10.0 g, 32.9 mmol) in THF (150 mL) was added ^nBuLi (1.6 M in hexanes, 41.1 mL, 65.7 mmol) dropwise at rt and stirred for 15 min. The solution was then cooled to –20 ^oC whereupon a solution of oxirane () (5.7 g, 27 mmol) in THF (40 mL) was added. After stirring at –10 ^oC for 45 min the reaction was quenched by the addition of saturated NH_4Cl solution (75 mL) followed by H_2O (100mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed successively with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column

chromatography eluting with Et_2O:petrol (1:2 then 1:1) afforded the title compound as a pale yellow oil. (10.37 g, 72%); R_f (Et_2O:petrol, 1:2), 0.25; $[\alpha]_D^{25}$ +7.8 (*c* 2.65, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3452br (OH), 2941s, 2864s, 1612m, 1586w, 1513s; δ_H (400 MHz; $CDCl_3$) 1.04-1.09 (3H, m, Si(C*H*$(CH_3)_2)_3$) overlapping with 1.07 (18H, s, Si(CH(C*H*$_3)_2)_3$), 1.70-1.84 (2H, m, 3-H_A, 3-H_B), 1.92-2.06 (2H, m, 5'-H_A, 5'-H_B), 2.02 (1H, dd, *J* 15.2, 1.8, 1-H_A), 2.22-2.28 (1H, m, 1''-H_A), overlapping with 2.26 (1H, dd, *J* 15.2, 9.0, 1-H_B), 2.37 (1H, m, 1''-H_B), 2.76-2.92 (4H, m, 4'-H_A, 4'-H_B, 6'-H_A, 6'-H_B), 3.59-3.63 (2H, dt, *J* 6.2, 1.1, 4-H_A, 4-H_B) overlapping with 3.62 (1H, d, *J* 2.9, OH), 3.78 (3H, s, $ArOCH_3$), 3.84-3.90 (1H, m, 2''-H_A), 3.94-4.0 (1H, m, 2''-H_B), 4.19 (1H, m, 2-H), 4.44 (2H, s, OC*H*$_2$Ar), 6.86 (2H, d, *J* 8.5, Ar-*meta*-H), 7.25 (2H, d, *J* 8.4 Ar-*ortho*-H); δ_C (100 MHz; $CDCl_3$) 11.9 (Si(*C*H$(CH_3)_2)_3$), 18.0 (Si(CH(*C*H$_3)_2)_3$), 24.9 (5'-C), 26.1, 26.3 (4'-C, 6'-C), 37.9 (3-C), 41.8 (1''-C), 46.0 (1-C), 50.9 (2'-C), 55.2 ($ArOCH_3$), 59.8 (2''-C), 66.8 (2-C), 67.5 (4-C), 72.8 (OCH_2Ar), 113.8 (Ar-*meta*-C), 129.2 (Ar-*ortho*-H), 130.4 (Ar-*ipso*-C) and 159.1 (Ar-*para*-C); Found (+ESI): $(MNa)^+$, 551.2675. $C_{27}H_{48}O_4SiS_2Na$ requires 551.2661.

(4'*R*,6'*S*)-Triisopropyl-(2-{6'-[2''-(p-methoxybenzyloxy)-ethyl]-2',2'-dimethyl-[1',3']-dioxan-4'-yl}-ethoxy)-silane (18)

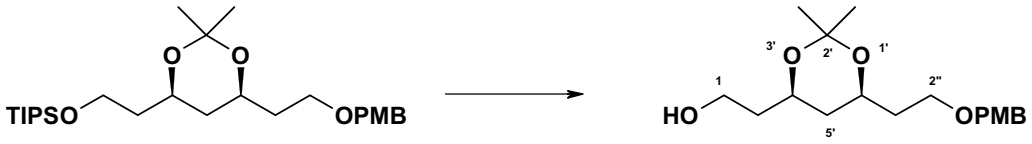


17 **18**

To a stirred suspension of dithiane **17** (1.14 g, 2.16 mmol) in MeCN (16 mL) and saturated $NaHCO_3$ solution (16 mL) at 0 ^oC was added iodine (2.19 g, 8.62 mmol) portionwise over 20 min. The reaction mixture was warmed to rt over 30 min. After this time the reaction was quenched with 1:1 solution of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$. The reaction mixture was extracted with Et_2O (4 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in*

vacuo. The crude hydroxy ketone was dissolved in THF (25 mL) and MeOH (5 mL) then cooled to –78 °C. To the solution was added $Et_2B(OMe)$ (2.8 mL, 2.8 mmol) and the reaction mixture was stirred for 1 h. After this time $NaBH_4$ (204 mg, 5.39 mmol) was added portionwise over 10 min. After stirring at –78 °C for a further 1 h, $NaBH_4$ (100 mg) added and reaction was stirred overnight at –78 °C. To the reaction mixture was added AcOH (5 mL) followed by H_2O (100 mL). The reaction mixture was extracted with Et_2O (3 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resultant oil was azeotroped with 10%AcOH/MeOH (3 x 40 mL) then with toluene (3 x 40 mL). The crude diol was dissolved in acetone (40 mL) and 2,2-dimethoxypropane (10 mL) and *para*-toluenesulfonic acid monohydrate (42 mg, 10 mol%) was added at 0 °C. The reaction mixture was stirred at this temperature for 1 h before it was quenched by the addition of saturated $NaHCO_3$ solution (50 mL) and then acetone removed *in vacuo*. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:9 then gradient to 1:2) to yield the title compound () as a colourless oil (6.02 g 70% over 3 steps); R_f (Et_2O:petrol 1:6) 0.24; $[\alpha]_D^{25}$ -1.5 (*c* 0.6, $CHCl_3$) ν_{max} (thin film)/cm^{-1} 2941s, 2864s, 1613m (Ar C=C), 1586w (Ar C=C), 1513s (Ar C=C); $[\alpha]_D^{25}$ -1.5, (*c* 0.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1.06 (21H, m, $Si(CH(CH_3)_2)_3$ and $Si(CH(CH_3)_2)_3$), 1.18 (1H, ap.q, *J* 11.8, 5'-H_A), 1.36 (3H, s, 2'-CCH_3), 1.42 (3H, s, 2'-CCH_3), 1.51 (1H, ap.dt, *J* 12.8, 2.5, 5'-H_B), 1.60-1.81 (4H, m, 2-H_A, 2-H_B, 1''-H_A, 1''-H_B), 3.48-3.59 (2H, m, 2''-H_A, 2''-H_B), 3.69-3.75 (1H, m, 1-H_A), 3.78-3.84 (1H, m, 1-H_B) overlapping with 3.81 (3H, s, $ArOCH_3$), 4.01-4.09 (2H, m, 4'-H and 6'-H), 4.43 (2H, ap. q, *J* 11.6, OCH_2Ar), 6.87 (2H, d, *J* 8.5 Ar-*meta*-H), 7.25 (2H, d, *J* 8.1, Ar-*ortho*-H); δ_C (100 MHz; $CDCl_3$) 12.0 ($Si(CH(CH_3)_2)_3$), 18.0 ($Si(CH(CH_3)_2)_3$), 19.8 (2'-CCH_3), 30.3 (2'-CCH_3), 36.3 (5'-C), 37.4 (1''-C), 39.7 (2-C), 55.3 ($ArOCH_3$), 59.1 (1-C), 65.7 (4'-C), 66.0 (2''-C), 66.2 (6'-C), 72.6 (OCH_2Ar), 98.5 (2'-C), 113.8 (Ar-*meta*-C), 129.2 (Ar-*ortho*-H), 130.7 (Ar-*ipso*-C) and 159.2 (Ar-*para*-C); Found (+ESI): $(MNa)^+$, 503.3158. $C_{27}H_{48}O_5SiNa$ requires 503.3169.

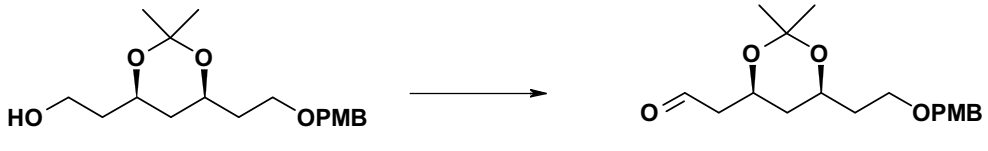
(4*R*',6*S*')-2-{6'-[2''-(*p*-Methoxybenzyloxy)-ethyl]-2',2'-dimethyl-[1',3']-dioxan-4'-yl}-ethanol (19)



18 **19**

To a solution of acetonide **18** (3.0 g, 6.24 mmol) in THF (20 mL) was added tetra *n*-butylammonium fluoride (1 M solution in THF, 6.86 mL, 6.86 mmol) at rt. After 1 h the reaction was diluted with Et_2O (30 mL) and quenched with saturated NH_4Cl solution (30 mL). The aqueous layer was separated and extracted with Et_2O (4 x 30 mL). The combined organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol, (1:2 then 1:1) afforded title compound (1.52 g, 75%) as a colourless oil; R_f (Et_2O:petrol, 1:1) 0.12; $[\alpha]_D^{25}$ -7.2 (*c* 1.1, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3439br (OH), 1612m (Ar C=C), 1586w (Ar C=C), 1512s (Ar C=C); δ_H (400 MHz; $CDCl_3$) 1.27 (1H, ap. td, *J* 20.9, 19.4, 5'-H_A), 1.37 (3H, s, 2'-CCH_3), 1.43-1.45 (1H, m, 5'-H_B) overlapping with 1.44 (3H, s, 2'-CCH_3), 1.67-1.78 (4H, m, 2-H_A, 2-H_B, 1''-H_A, 1''-H_B), 2.54 (1H, dd, *J* 6.0, 4.2, OH), 3.49 (1H, m, 2''-H_A), 3.54 (1H, m, 2''-H_B), 3.75 (2H, m, 1-H_A, 1-H_B), 4.01-4.12 (2H, m, 6'-H and 4'-H), 4.42 (2H, ap. q, *J* 12.2, OCH_2Ar), 6.87 (2H, d, *J* 8.5, Ar-*meta*-H), 7.25 (2H, d, *J* 8.5, Ar-*ortho*-H); δ_C (100 MHz; $CDCl_3$) 20.0 (2'-C*C*H_3), 30.0 (2'-C*C*H_3), 34.6 (1''-C), 36.3 (5'-C), 38.1 (2-C), 55.3 ($ArOCH_3$), 60.9 (1-C), 65.8 (2''-C), 66.2 (6'-C), 69.5 (4'-C), 72.6 (OCH_2Ar), 98.6 (2'-C), 113.8 (Ar-*meta*-C), 129.2 (Ar-*ortho*-H), 130.6 (Ar-*ipso*-C) and 159.2 (Ar-*para*-C); Found (+ESI): $(MNa)^+$ 347.19. $C_{18}H_{28}O_5$ requires 347.1052.

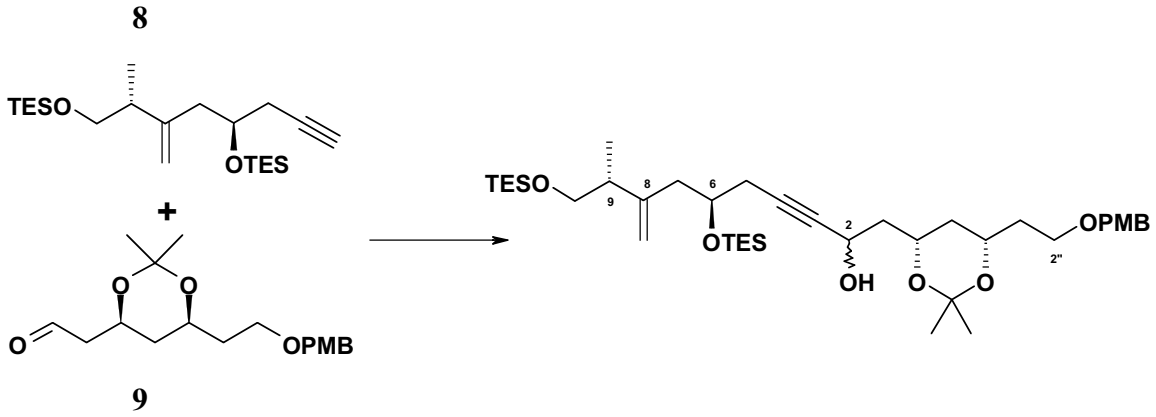
(4'*R*,6'*S*)-{6'-[2''-(*p*-methoxybenzyloxy)-ethyl]-2',2'-dimethyl-[1',3']-dioxan-4'-yl}-acetaldehyde (9)



19 **9**

To a solution of oxalyl chloride (0.806 mL, 9.24 mmol) in CH_2Cl_2 (20 mL) at –78 ^oC was added DMSO (0.65 mL, 9.24 mmol). The resulting solution was stirred at this temperature for 30 min. To the reaction mixture was added a solution of alcohol **19**(1.00 g, 3.08 mmol) in CH_2Cl_2 (15 mL) and stirred for 2 h. To the solution was then added TEA (4.3 mL, 30.8 mmol, 10 eq) and the reaction mixture warmed to –20 ^oC over 45 min. The reaction was quenched with H_2O (20 mL) at 0 ^oC and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol, (1:2 then 1:1) afforded the title compound (846 mg, 85%) as a colourless oil; R_f (Et_2O:petrol, 1:1) 0.43. The product was used immediately without further characterisation.

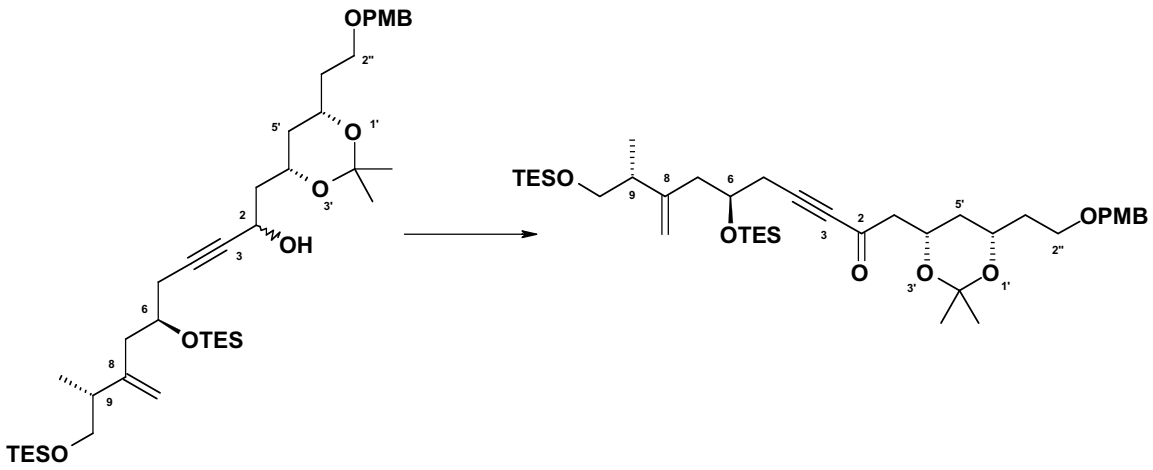
(2*RS*,6*S*,9*R*,4'*R*,6'*S*)1-{6'-[2''-(*p*-Methoxybenzyloxy)-ethyl]-2',2'-dimethyl-[1',3']-dioxan-4'-yl}-9-methyl-8-methylene-6,10-bistriethylsilanyloxy-dec-3-yn-2-ol



To a solution of alkyne **8** (1.47 g, 3.7 mmol) in THF (20 mL) at 0 ^oC was added ^iPrMgCl (2.0 M solution in THF, 1.85 mL, 3.7 mmol) and stirred for 90 min. After this time the

solution was cooled to –10 °C and solution of freshly prepared aldehyde **9** (846 mg, 3.0 mmol) in THF (20 mL) was added. The reaction mixture was stirred for 1 h before quenching with saturated $NaHCO_3$ solution (50 mL) and extracting with EtOAc (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:3 then 1:1) yielded the title compound as mixture of diastereoisomers at C-2, (1.46 g, 77%); R_f (Et_2O:petrol, 1:1) 0.59, 0.62; Found (+ESI): $(MNa)^+$ 741.4556. $C_{40}H_{70}O_7Si_2Na$ requires 741.4558.

(6*S*,9*R*,4'*S*,6'*S*)1-{6'-[2''-(*p*-Methoxybenzyloxy)-ethyl]-2',2'-dimethyl-[1',3']-dioxan-4'-yl}-9-methyl-8-methylene-6,10-bistriethylsilanyloxy-dec-3-yn-2-one (7)

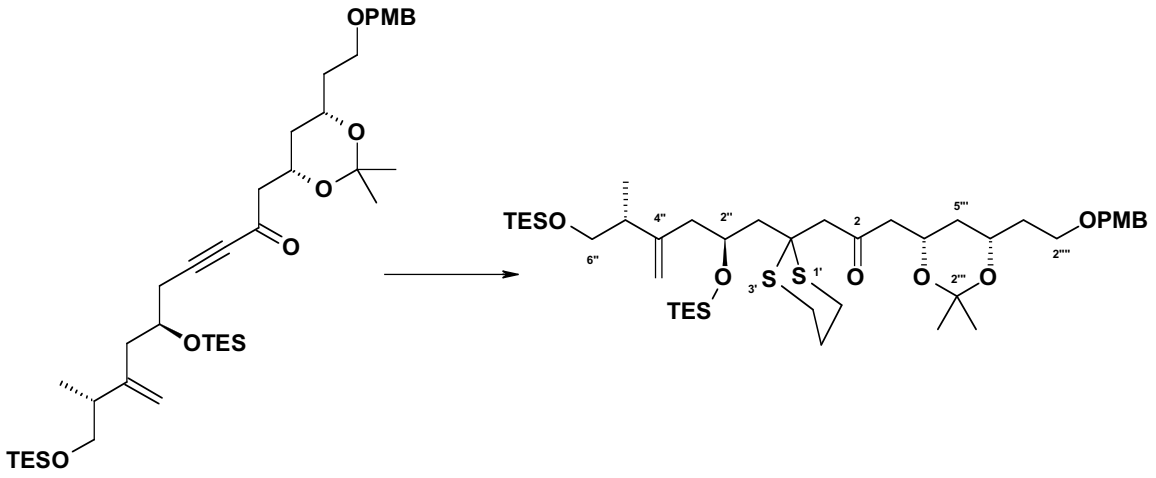


7

To a solution of alcohol (1.45 g 2.01 mmol) in CH_2Cl_2 (40 mL) was added Dess-Martin periodinane (1.11 g, 2.62 mmol) at 0 °C. After 2 h at rt a further aliquot of Dess-Martin periodinane (600 mg) was added (0.3 eq). The reaction was quenched after a further 75 min with 1:1 solution of saturated $NaHCO_3$ and $Na_2S_2O_3$ (75 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Flash column chromatography eluting with Et_2O:petrol:TEA (1:2:0.5% then 1:1:0.5%) yielded the title compound as a yellow oil

(1.29 g, 90%); R_f (Et_2O:petrol, 1:2) 0.52; $[\alpha]_D^{25}$ -1.0; (*c* 1.05, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954s, 2876s, 2214w (C≡C), 1674m (C=C), 1613w (C=O); δ_H (600 MHz; $CDCl_3$) 0.58 (6H, q, *J* 7.9, Si(C*H*$_2$CH$_3$)$_3$), 0.62 (6H, q, *J* 7.9, Si(C*H*$_2$CH$_3$)$_3$), 0.95 (9H, t, *J* 7.9, Si(CH$_2$C*H*$_3$)$_3$), 0.96 (9H, t, *J* 8.1, Si(CH$_2$C*H*$_3$)$_3$), 1.04 (3H, d, *J* 6.9, 9-CH$_3$), 1.17 (1H, ap. q (ddd), *J* 12.4, 11.6, 5'-H$_A$), 1.34 (3H, s, 2'C-CH$_3$), 1.43 (3H, s, 2'C-CH$_3$), 1.56 (1H, ap. dt, *J* 12.7, 2.4, 5'-H$_B$), 1.68-1.76 (2H, m, 1"-H$_A$ and 1"-H$_B$), 2.25 (1H, m, 9-H), 2.31 (2H, d, *J* 6.4, 7-H$_A$ and 7-H$_B$), 2.48 (1H, dd, *J* 17.2, 5.8, 5-H$_A$), 2.55 (1H, dd, *J* 16.2, 5.7, 1-H$_A$), 2.58 (1H, dd, *J* 17.3, 5.1, 5-H$_B$), 2.78 (1H, dd, *J* 16.2, 7.0, 1-H$_B$), 3.40 (1H, dd, *J* 9.7, 7.3, 10-H$_A$), 3.46-3.56 (2H, m, 2"-H$_A$ and 2"-H$_B$), 3.60 (1H, dd, *J* 9.8, 6.0, 10-H$_B$), 3.80 (3H, s, ArOCH$_3$), 4.02 (1H, ap. quin, *J* 5.7, 6-H) overlapping with 4.02-4.07 (1H, m, 6'-H), 4.42 (2H, ap. q, *J* 11.4, 5.7, OCH$_2$Ar) overlapping with 4.41-4.44 (1H, m, 4'-H), 4.87 (2H, s, 8-CH$_2$), 6.87 (2H, d, *J* 8.6, Ar-*meta*-H), 7.24 (2H, d, *J* 8.5, Ar-*ortho*-H); δ_C (150 MHz; $CDCl_3$) 4.4 (Si(*C*H$_2$CH$_3$)$_3$), 4.9 (Si(*C*H$_2$CH$_3$)$_3$), 6.7 (Si(CH$_2$*C*H$_3$)$_3$), 6.8 (Si(CH$_2$*C*H$_3$)$_3$), 16.8 (9-CH$_3$), 19.7 (2'C*C*H3), 27.3 (5-C), 30.0 (2'C*C*H3), 36.5 (1"-C), 36.6 (5'-C), 42.1 (9-C), 43.6 (7-C), 51.9 (1-C), 55.2 (ArOCH$_3$), 65.3 (4'-C), 65.8 (2"-C), 65.9 (6'-C), 67.2 (10-C), 69.3 (6-C), 72.6 (OCH$_2$Ar), 82.5 (4-C), 92.1 (3-C), 98.8 (2'-C), 112.1 (8-*C*H$_2$), 113.8 (Ar-*meta*-C), 129.2 (Ar-*ortho*-H), 130.6 (Ar-*ipso*-C), 148.2 (8-C), 159.2 (Ar-*para*-C) and 184.8 (2-C); Found (+ESI): $(MNa)^+$ 739.4389. $C_{40}H_{68}O_7Si_2Na$ requires 739.4401.

(2''*R*,5''*S*,4'''*S*,6'''*S*)1-{6'''-[2''''-(*p*-Methoxybenzyloxy)-ethyl]-2''',2'''-dimethyl-[1''',3''']-dioxan-4'''-yl}-3-[2'-(5''-methyl-4''-methylene-2'',6''-bis-triethylsilanyloxy-hexyl)-[1',3']-dithian-2'-yl]-propane-2-one (6)

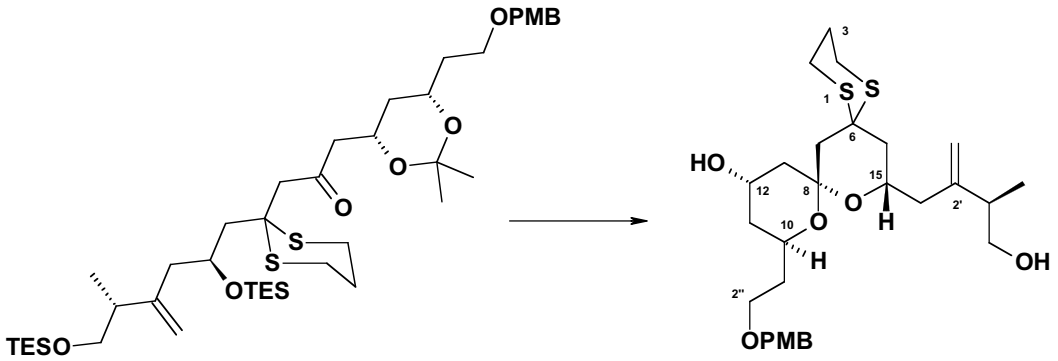


7 **6**

To a solution of ynone **7** (1.26 g, 1.76 mmol) in CH_2Cl_2 (6 mL) and MeOH (18 mL) at –10 ^oC was added 1,3-propanedithiol (0.22 mL, 2.2 mmol) followed by NaOMe (128 mg) and the reaction mixture was stirred at –10 ^oC overnight. The reaction was quenched with saturated NH_4Cl solution (40 mL) and extracted with Et_2O (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol:TEA (1:19:0.5% then 1:9:0.5%) afforded the title compound as a yellow oil (1.18 g, 81%); R_f (Et_2O:petrol, 1:1) 0.45; $[\alpha]_D^{25}$ +12.6; (*c* 0.27, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2953m, 2875m, 1717br (C=O), 1613w (C=C), 1513; δ_H (600 MHz; $CDCl_3$) 0.59 (6H, q, *J* 7.9, Si(C*H*$_2$CH$_3$)$_3$), 0.64 (6H, q, *J* 7.9, Si(C*H*$_2$CH$_3$)$_3$), 0.96 (9H, t, *J* 7.8, Si(CH$_2$C*H*$_3$)$_3$), 0.97 (9H, t, *J* 7.8, Si(CH$_2$C*H*$_3$)$_3$), 1.09 (3H, d, *J* 6.8, 5"-CH_3), 1.14 (1H, ap. q (ddd), *J* 12.5, 11.6, 5'"-H_A), 1.34 (3H, s, 2'"-CH_3), 1.43 (3H, s, 2'"-CH_3), 1.63 (1H, ap. dt, *J* 12.7, 2.3, 5'"-H_B), 1.68-1.76 (2H, m, 1""-H_A and 1""-H_B), 1.93 (2H, ap. t, *J* 3.4, 5'-H_A and 5'-H_B), 2.20 (1H, dd, *J* 9.3, 4.7, 1"-H_A), 2.25-2.30 (2H, m, 5"-H and 3"-H_A), 2.33-2.39 (2H, m, 3"-H_B and 1"-H_B), 2.56 (1H, dd, *J* 10.1, 6.2, 1-H_A), 2.72 (1H, dd, *J* 16.4, 6.1, 1-H_B) overlapping with 2.74-2.81 (4H, m, 4'-H_A, 4'-H_B, 6'-H_A and 6'-H_B), 3.13 (1H, ap.d, *J* 15.8, 3-H_A), 3.23 (1H, ap. d, *J* 15.8, 3-H_B), 3.39 (1H, dd, *J* 9.7, 8.1, 6"-H_A), 3.50-3.55 (2H, m, 2""-H_A and 2""-H_B), 3.66 (1H, dd, *J* 9.9, 5.0, 6"-H_B), 3.80 (3H, s, ArOCH_3), 4.03 (1H, m, 6'"-H), 4.26-4.30 (1H, m, 2"-H) overlapping with 4.30-4.35 (1H, m, 4'"-H), 4.42 (2H, q, *J* 11.6, 9.9, OCH_2Ar), 4.87 (2H,

d, *J* 5.3, 4"-CH_AH_B), 6.88 (2H, d, *J* 8.7, Ar-*meta*-H), 7.26 (2H, d, *J* 8.7, Ar-o*rtho*-H); δ_C (150 MHz; $CDCl_3$) 4.4 (Si(CH_2CH_3)$_3$), 5.5 (Si(CH_2CH_3)$_3$), 6.8 (Si(CH_2CH_3)$_3$), 7.0 (Si(CH_2CH_3)$_3$), 16.8 (5"-C), 19.8 (2"'-CH_3), 24.9 (5'-C), 26.3 (4'-C), 26.6 (6'-C), 30.1 (2"'-CH_3), 36.5 (1""-C), 36.9 (5"'-C), 42.5 (5"-C), 44.0 (3"-C), 45.0 (1"-C), 49.5 (2'-C), 50.9 (1-C), 52.0 (3-C), 55.3 ($ArOCH_3$), 65.7 (2""-C), 65.9 (6"'-C), 66.0 (6"-C), 67.0 (2"-C), 69.8 (4"'-C), 72.6 (OCH_2Ar), 98.7 (2"'-C), 111.8 (4"-CH_2), 113.8 (Ar-*meta*-C), 129.2 (Ar-*ortho*-H), 130.7 (Ar-*ipso*-C), 148.8 (4"-C), 159.1 (Ar-*para*-C) and 204.5 (2-C); Found (+ESI): $(MNa)^+$ 847.4482. $C_{43}H_{76}O_7S_2Si_2Na$ requires 847.4469.

(8*R*,10*S*,12,*S*,15*S*,3'*R*)-15-(4'-Hydroxy-3'-methyl-2'-methylene-butyl)-10-[2''-(*p*-methoxybenzyloxy)-ethyl]-9,14-dioxa-1,5-dithia-dispiro[5.1.5.3]hexadecane-12-ol. (20)

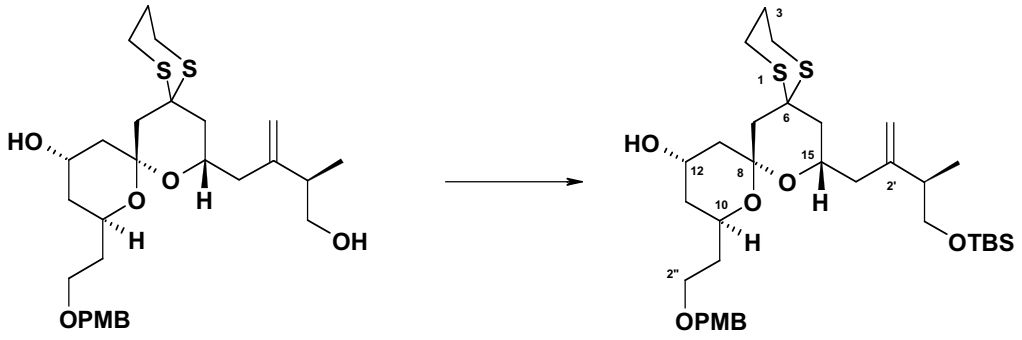


6 **20**

To a rapidly stirring solution of ketone **6** (1.35 g, 1.63 mmol) in CH_2Cl_2 (10 mL) and MeCN (10 mL) at 0 ^oC was added perchloric acid (10% v/v in H_2O, 2.5 mL). After 30 min the reaction mixture was neutralised with saturated $NaHCO_3$ solution (50 mL) and extracted with Et_2O (4 x 50 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Flash column chromatography eluting with Et_2O yielded the title compound as a colourless oil (581 mg, 61%); R_f(Et_2O) 0.26; $[\alpha]_D^{25}$ -30.3; (*c* 0.38, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3499br (OH), 2909m, 1642w, 1611m (C=C), 1512s; δ_H (600 MHz; $CDCl_3$) 1.01 (3H, d, *J* 6.9, 3'-CH_3), 1.43 (1H, ap. dt,

J 11.9, 2.6, 11-H_{ax}), 1.60-1.65 (3H, m, 7-H_{ax}, 16-H_{ax}, 12-OH), 1.68-1.81 (6H, m, 13-H_{eq}, 11-H_{eq}, 16-H_{eq}, 1''-H_A, 1''-H_B, 4'-OH), 1.88 (1H, m, 3-H_A), 2.05 (1H, m, 3-H_B), 2.15 (1H, dd, *J* 14.2, 1.9 13-H_{ax}), 2.24 (2H, ap. d, *J* 6.8, 1'-H_A and 1'-H_B), 2.30 (1H, ap. ddd, *J* 12.9, 6.5, 6.5, 3'-H), 2.55 (1H, ap. d, *J* 13.7, 7-H_{eq}) overlapping with 2.57 (1H, dt, *J* 14.6, 3.9, 2-H_A or 4-H_A), 2.70 (1H, dt, *J* 14.3, 3.4, 2-H_A or 4-H_A), 2.87 (1H, ddd, *J* 14.6, 7.6, 3.9, 2-H_B or 4-H_B), 3.07 (1H, ddd, *J* 14.1, 7.6, 2.9, 2-H_B or 4-H_B), 3.36 (1H, dd, *J* 10.8, 6.6, 4'-H_A), 3.44 (1H, dd, *J* 16.9, 6.9, 4'-H_B), 3.61 (1H, m, 2''-HA), 3.80 (3H, s, $ArOCH_3$), 3.82 (1H, m, 2''-H_B), 3.97 (1H, ap. t, *J* 9.2, 10-H), 4.02 (1H, ap. s, 12-H), 4.19 (1H, m, 15-H), 4.42 (2H, m, OCH_2Ar), 4.94 (1H, s, 2'-CH_A), 4.99 (1H, s, 2'-CH_B), 6.86 (2H, d, *J* 8.5, Ar-meta-H), 7.25 (2H, d, *J* 8.5, Ar-ortho-H); δ_C (150 MHz; $CDCl_3$) 16.2 (3'-CH_3), 25.1 (3-C), 26.3 and 26.4 (2-C and 4-C), 35.6 (1''-C), 38.1 (11-C), 40.1 (16-C), 41.0 (3'-C), 41.8 (1'-C), 42.1 (7-C), 46.3 (13-C), 46.8 (6-C), 55.3 ($ArOCH_3$), 61.7 (10-C), 64.9 (12-C), 65.4 (15-C), 66.2 (4'-C), 66.5 (2''-C), 72.3 (OCH_2Ar), 98.8 (8-C), 113.1 (2'-CH_2), 113.7 (Ar-*meta*-C), 129.4 (Ar-*ortho*-C), 130.7 (Ar-*ipso*-C), 147.6 (2'-C), 159.1 (Ar-*para*-C); Found (+ESI): $(MNa)^+$ 561.2355. $C_{28}H_{42}O_6S_2Na$ requires 561.2321.

(8*R*,10*S*,12,*S*,15*S*,3'*R*)-15-(4'-(*tert*-Butyldimethyl-silanoxy)-3'-methyl-2'-methylene-butyl)-10-[2''-(*p*-methoxybenzyloxy)-ethyl]-9,14-dioxa-1,5-dithia-dispiro[5.1.5.3]hexadecane-12-ol (21)

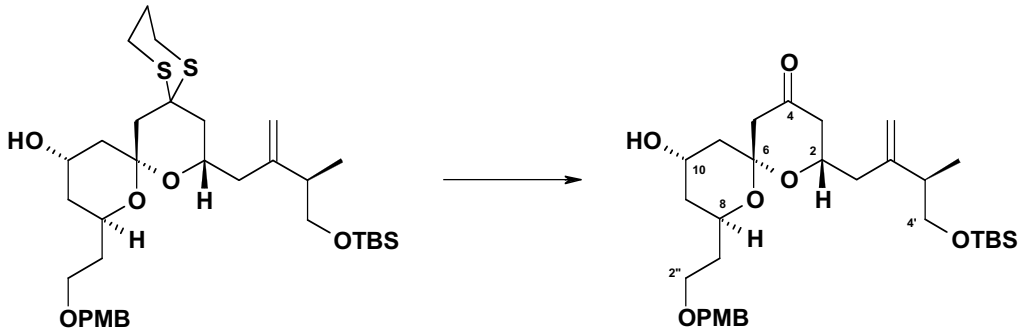


20 **21**

To a solution of spiro-alcohol **20** (560 mg, 1.04 mmol) in THF (20 mL) at rt was added imidazole (106 mg, 1.56 mmol) and TBSCl (204 mg, 1.35 mmol) and the reaction mixture was stirred overnight. A further portion of imidazole (92 mg) and TBSCl (160

mg) added and the reaction mixture was stirred for a further 3 h. The reaction was quenched with saturated NH_4Cl solution (50 mL) and extracted with Et_2O (4 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Flash column chromatography eluting with Et_2O:petrol (1:4 then1:1) yielded the title compound as a colourless oil (644 mg, 95%); R_f (Et_2O:petrol, 1:1) 0.3; $[\alpha]_D^{25}$ -4.9; (*c* 0.45, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3501br (OH), 2930m, 2857m, 2246w, 1612m (C=C), 1512m; δ_H (600 MHz; $CDCl_3$) 0.03 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.05 (3H, d, *J* 6.9, 3'-CH_3) 1.41 (1H, m, 11-H_{ax}), 1.57-1.66 (2H, m, 13-H_{ax}, 16-H_{ax}), 1.69-1.77 (4H, m, 7-H_{ax}, 11-H_{eq}, 1''-H_A and 1''-H_B), 1.81 (1H, ap. dt, *J* 15.8, 1.9, 13-H_{eq}), 1.83-1.89 (1H, m, 3-H_A) 2.04 (1H, m, 3-H_B), 2.15 (1H, dd, *J* 14.2, 1.4, 7-H_{eq}), 2.24-2.33 (2H, m, 1'-H_A and 1'-H_B), 2.36 (1H, ap. ddd, *J*, 12.9, 6.5, 6.5, 3'-H), 2.51 (1H, ap. d, *J* 13.9, 16-H_{eq}), 2.52-2.56 (1H, dt, *J* 7.6, 3.6, 2-H_A or 4-H_A), 2.69 (1H, dt, *J* 14.5, 3.4, 2-H_A or 4-H_A), 2.83 (1H, ddd, *J* 14.5, 7.6, 2.7, 2-H_B or 4-H_B), 3.06 (1H, ddd, *J* 14.0, 7.6, 2.9, 2-H_B or 4-H_B), 3.37 (1H, dd, *J* 9.7, 6.8, 4'-H_A), 3.53 (1H, dd, *J* 9.8, 5.6, 4'-H_B), 3.64-3.70 (2H, m, 2''-H_A and 2''-H_B), 3.79 (3H, s, $ArOCH_3$), 3.89-3.93 (2H, m, 10-H and 12-OH), 3.99 (1H, m, 12-H), 4.16 (1H, m, 15-H), 4.37-4.48 (2H, OCH_AH_BAr), 4.91 (2H, d, *J* 3.1, 2'-CH_AH_B), 6.85 (2H, d, *J* 8.5, Ar-meta-H), 7.23 (2H, d, *J* 8.5, Ar-ortho-H); δ_C (150 MHz; $CDCl_3$) –5.40 ($Si(CH_3)_2$), 16.2 (3'-CH_3), 18.3 ($SiC(CH_3)_3$), 25.1 (3-C), 25.9 ($SiC(CH_3)_3$), 26.3 and 26.4 (2-C and 4-C), 35.8 (1''-C), 38.1 (11-C), 40.1 (13-C), 40.6 (3'-C) 42.2 (1'-C), 42.2 (16-C), 46.4 (7-C), 46.8 (6-C), 55.2 ($ArOCH_3$), 62.0 (10-C), 64.9 (12-C), 65.2 (15-C), 66.8 (2''-C), 68.2 (4'-C), 72.4 (OCH_2Ar), 98.7 (8-C), 112.2 (2'-CH_2), 113.7 (Ar-*meta*-C), 129.2 (Ar-*ortho*-C), 130.9 (Ar-*ipso*-C), 148.2 (2'-C), 159.0 (Ar-*para*-C); Found (+ESI): $(MNa)^+$ 675.3187. $C_{34}H_{56}O_6S_2SiNa$ requires 675.3185.

(2*S*,6*R*,8*S*,10*S*,3'*R*)-2-[4'-(*tert*-Butyldimethylsilanyloxy)-3'-methyl-2'-methylene-butyl]-10-hydroxy-8-[2''-(*p*-methoxybenzyloxy)-ethyl]-1,7-dioxa-spiro[5.5]undecan-4-one

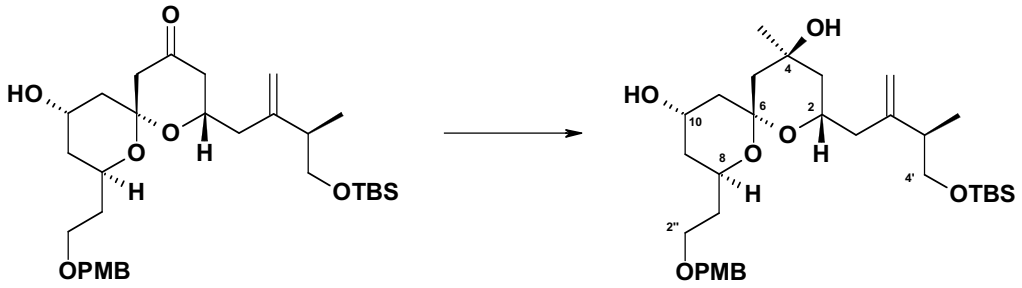


21

To a stirring suspension of dithiane **21** (638 mg, 0.98 mmol) in MeCN (15 mL) and saturated $NaHCO_3$ solution (15 mL) at 0 ^oC was added iodine (992 mg, 3.9 mmol) portionwise. After 30 min, the reaction was quenched with 1:1 solution of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ (50 mL) and extracted with Et_2O (3 x 75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (2:1 then 3:1) afforded the title compound as a colourless oil (485 mg, 88%); R_f (Et_2O:petrol, 4:1) 0.32; $[\alpha]_D^{25}$ -8.2; (*c* 1.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3519br (OH), 2928m, 2856m, 2244w, 1725s (C=O), 1612m (C=C), 1513s; δ_H (600 MHz; $CDCl_3$) 0.00 (6H, s, $Si(CH_3)_2$), 0.86 (9H, s, $SiC(CH_3)_3$), 1.03 (3H, d, *J* 6.9, 3'-CH_3), 1.39 (1H, ap. dd, *J* 12.8, 2.5, 9-H_{ax}), 1.61 (1H, dd, *J* 14.2, 3.4, 11-H_{ax}), 1.65-1.75 (3H, m, 1"-H_A, 1"-H_B and 9-H_{eq}), 2.03 (1H, ap. d, *J* 14.2, 11-H_{eq}), 2.20 (1H, dd, *J* 14.1, 11.3, 1'-H), 2.27-2.35 (4H, m, 1'-H, 3-H_{ax}, 3-H_{eq}, 3'-H), 2.40 (2H, ap. d, *J* 14.4, 5-H_{ax} and 5-H_{eq}), 3.34 (1H, dd, *J* 9.6, 6.5, 4'-H_A), 3.40 (1H, m, 2"-H_A), 3.47 (1H, dd, *J* 9.6, 5.6, 4'-H_B), 3.51 (1H, ddd, *J* 14.4, 9.0, 5.4, 2"-H_B), 3.78 (1H, d, *J* 12.3, 10-OH), 3.79 (3H, s, $ArOCH_3$), 3.90-3.95 (1H, m, 8-H), 4.02 (1H, ap. dt, *J* 10.4, 1.9, 10-H), 4.09 (1H, m, 2-H), 4.38 (2H, ap. q, *J* 11.8, 8.2, OCH_2Ar), 4.94 (2H, d, *J* 13.7, 2'-CH_2), 6.85 (2H, d, *J* 8.5, Ar-meta-H), 7.23 (2H, d, *J* 8.5, Ar-ortho-H); δ_C (150 MHz; $CDCl_3$) –5.40 ($Si(CH_3)_2$), 16.1 (3'-CH_3), 18.2 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 35.6 (1"-C), 37.6 (9-C), 39.5 (11-C), 40.4 (3'-C), 43.4 (3-C), 46.8 (1'-C), 51.4 (5-C), 55.2 ($ArOCH_3$), 61.8 (8-C), 64.2 (10-C), 65.5 (2"-C), 67.7 (2-C), 68.2 (4'-C), 72.5 (OCH_2Ar), 100.7 (6-C), 112.7 (2'-CH_2), 113.7 (Ar-*meta*-C), 129.4 (Ar-*ortho*-C), 130.4 (Ar-*ipso*-C), 147.9 (2'-C), 159.1

(Ar-*para*-C), 204.2 (4-C); Found (+ESI): $(MNa)^+$ 585.3213. $C_{31}H_{50}O_7SiNa$ requires 585.3224.

(2*S*,4*S*,6*R*,8*S*,10*S*,3'*R*)-2-[4'-(*tert*-Butyldimethylsilanyloxy)-3'-methyl-2'-methylene-butyl]-8-[2''-(*p*-methoxybenzyloxy)-ethyl]-4-methyl-1,7-dioxa-spiro[5.5]undecane-4,10-diol (22)

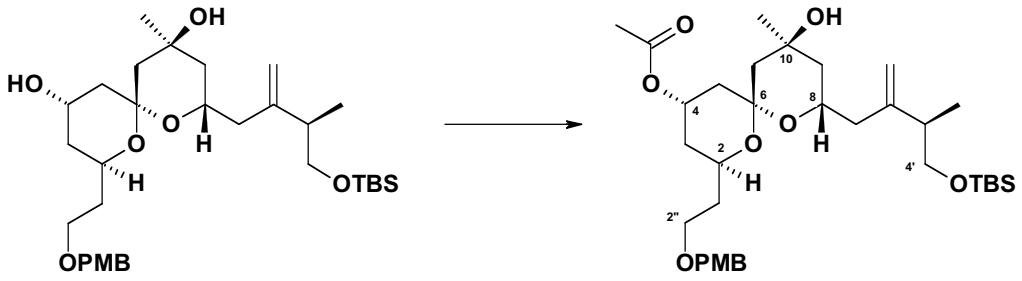


22

Solid cerium chloride heptahydrate (3.64 g, 9.77 mmol) was dried overnight at 160 ^oC under high vacuum. The solid was cooled to rt and dissolved in THF (15 mL) and stirred for 2 h. After which time the suspension was cooled to –78 ^oC and MeLi (1.6 M solution in Et_2O, 4.8 mL, 7.68 mmol) was added. The reaction mixture was then stirred at –78 ^oC for 1 h, before the addition of ketone (480 mg, 0.85 mmol) in THF (10 mL). The reaction was quenched after 20 min with saturated NH_4Cl solution (30 mL) and extracted with Et_2O (5 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (2:1 then 3:1) afforded the title compound as a colourless oil (447 mg, 90%); R_f (Et_2O:petrol, 4:1) 0.45; $[\alpha]_D^{25}$ -3.9; (*c* 0.5, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3486br (OH), 2929m, 2857m, 2349w, 1612m, 1513s; δ_H (600 MHz; $CDCl_3$) 0.02 (6H, s, $Si(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.05 (3H, d, *J* 6.9, 3'-CH_3), 1.19 (3H, s, 4-CH_3), 1.32 (1H, dd, *J* 12.6, 12.4, 3-H_{ax}), 1.43-1.50 (2H, m, 5-H_{eq} and 9-H_{ax}), 1.62 (1H, ap. d, *J* 14.5, 11-H_{ax}), 1.66-1.82 (6H, m, 3-H_{eq}, 1''-H_A, 1''-H_B, 5-H_{ax}, 9-H_{eq} and 11-H_{eq}), 2.20 (1H, dd, *J* 13.8, 9.7, 1'-H_A), 2.25-2.30 (2H, m, 1'-H_B and 3'-H), 3.32 (1H, dd, *J* 9.6, 6.7, 4'-H_A), 3.45-3.52 (3H, m, 4'-

H_B, 2''-H_A and 2''-H_B), 3.79 (3H, s, $ArOCH_3$), 3.99-4.02 (3H, m, 8-H, 10-H and 10-OH), 4.09 (1H, m, 2-H), 4.43 (2H, ap. q, *J* 15.6, 11.8, OCH_2Ar), 4.60 (1H, s, 4-OH), 4.91 (2H, d, *J* 9.0, 2'-CH_2), 6.85 (2H, d, *J* 8.5, Ar-meta-H), 7.25 (2H, d, *J* 8.5, Ar-ortho-H); δ_C (150 MHz; $CDCl_3$) –5.4 ($Si(CH_3)_2$), 16.2 (3'-CH_3), 18.3 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 30.0 (4-CH_3), 35.7 (1''-C), 38.3 (9-C), 39.8 (11-C), 40.3 (3'-C), 43.0 (1'-C), 44.0 (3-C), 45.5 (5-C), 55.2 ($ArOCH_3$), 63.2 (8-C), 64.4 (10-C), 64.5 (2-C), 66.6 (4'-C), 67.6 (2''-C), 68.1 (4-C), 72.7 (OCH_2Ar), 100.0 (6-C), 112.2 (2'-CH_2), 113.7 (Ar-*meta*-C), 129.7 (Ar-*ortho*-C), 130.2 (Ar-*ipso*-C), 148.4 (2'-C), 159.2 (Ar-*para*-C); Found (+ESI): $(MNa)^+$ 601.3553. $C_{32}H_{54}O_7SiNa$ requires 601.3537.

(2*S*,4*S*,6*R*,8*S*,10*S*,3'*R*) Acetic acid-8-[4-(*tert*-butyldimethylsilanyloxy)-3-methyl-2-methylene-butyl]-10-hydroxy-2-[2-(p-methoxybenzyloxy)-ethyl]-10-methyl-1,7-dioxa-spiro[5.5]undec-4-yl ester

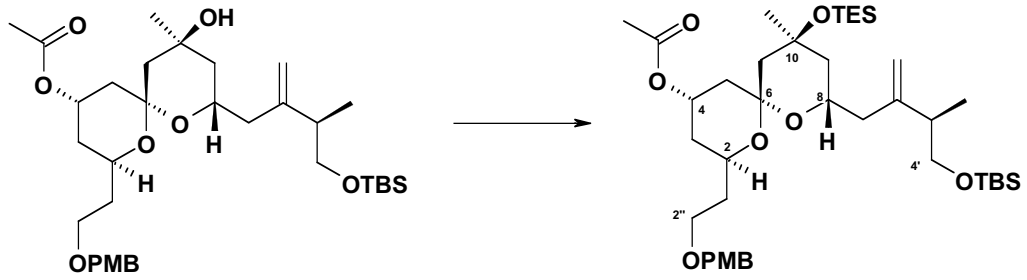


22

To a stirring solution of diol **22** (442 mg, 0.76 mmol) in CH_2Cl_2 (20 mL) was added Ac_2O (0.43 mL, 4.58 mmol), DMAP (186 mg, 1.52 mmol) and pyridine (0.61 mL, 7.6 mmol). The reaction was stirred for 3 days at rt. The reaction was quenched with saturated NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with saturated $CuSO_4$ solution (20 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Flash column chromatography eluting with Et_2O:petrol (1:1) yielded the title compound as a colourless oil (410 mg, 86%); R_f (Et_2O:petrol, 4:1) 0.68; $[\alpha]_D^{25}$ -32.6; (*c* 0.5, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2931s, 1734s (C=O), 1513m; δ_H (600 MHz; $CDCl_3$) 0.02 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.04 (3H, d, *J* 6.9, 3'-CH_3), 1.17 (3H, s, 10-CH_3), 1.26 (1H, dd, *J* 12.8, 12.2, 9-H_{ax}), 1.44 (1H, d, *J* 13.1, 11-H_{ax}), 1.54

(1H, ddd, *J* 14.6, 11.9, 3.2, 3-H_{ax}), 1.61 (1H, dd, *J* 15.1, 4.2, 5-H_{ax}), 1.66-1.80 (5H, m, 9-H_{eq}, 11-H_{eq}, 3-H_{eq}, 1''-H_A and 1''-H_B), 1.96 (1H, ap. dt, *J* 15.1, 1.4, 5-H_{eq}), 2.03 (3H, s, $COCH_3$), 2.16 (1H, dd, *J* 14.5, 5.4, 1'-H_A), 2.29-2.33 (2H, m, 1'-H_B and 3'-H), 3.36 (1H, dd, *J* 9.5, 7.4, 4'-H_A), 3.51 (2H, t, *J* 6.3, 2''-H_A and 2''-H_B), 3.58 (1H, dd, *J* 9.6, 5.4, 4'-H_B), 3.79 (3H, s, $ArOCH_3$), 4.05 (1H, m, 8-H), 4.16 (1H, m, 2-H), 4.43 (2H, s, OCH_2Ar), 4.53 (1H, s, OH), 4.83 (1H, s, 2'-CH_A), 4.94 (1H, s, 2'-CH_B), 5.02 (1H, m, 4-H), 6.85 (2H, d, *J* 8.5, Ar-meta-H), 7.24 (2H, d, *J* 8.5, Ar-ortho-H); δ_C (150 MHz; $CDCl_3$) –5.41 ($SiCH_3$), -5.39 ($SiCH_3$), 16.5 (3'-CH_3), 18.3 ($SiC(CH_3)_3$), 21.4 ($COCH_3$), 25.9 ($SiC(CH_3)_3$), 30.0 (10-CH_3), 34.7 (1''-C) 35.7 (3-C), 37.5 (5-C), 41.7 (3'-C), 41.9 (1'-C), 43.4 (9-C), 46.0 (11-C), 55.2 ($ArOCH_3$), 63.2 (2-C), 65.0 (8-C), 66.4 (4-C), 66.6 (2''-C), 67.7 (4'-C), 68.0 (10-C), 72.7 (OCH_2Ar), 98.0 (6-C), 111.4 (2'-CH_2), 113.7 (Ar-*meta*-C), 129.5 (Ar-*ortho*-C), 130.3 (Ar-*ipso*-C), 148.2 (2'-C), 159.1 (Ar-*para*-C) and 170.8 ($COCH_3$); Found (+ESI): $(MNa)^+$ 643.3640. $C_{34}H_{56}O_8SiNa$ requires 643.3642.

(2*S*,4*S*,6*R*,8*S*,10*S*,3'*R*) Acetic acid-8-[4'-(*tert*-butyldimethylsilanyloxy)-3'-methyl-2'-methylene-butyl-2-[2''-(*p*-methoxybenzyloxy)-ethyl]-10-methyl-10-triethylsilanyloxy-1,7-dioxa-spiro[5.5]undec-4-yl ester (23)

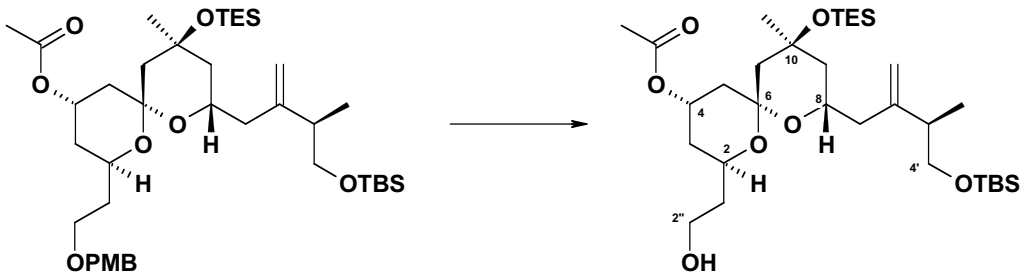


23

To a solution of alcohol (405 mg, 0.65 mmol) and 2,6-lutidine (0.45 mL, 3.91 mmol) in CH_2Cl_2 (15 mL) at –78 ^oC was added TESOTf (0.42 mL, 1.96 mmol). The reaction mixture was stirred for 30 min at 0 ^oC then quenched with saturated $NaHCO_3$ solution (25 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with

Et_2O:petrol (1:2) yielded the title compound as a colourless oil (438 mg, 92%); R_f (Et_2O:petrol, 2:1) 0.62; $[\alpha]_D^{25}$ -38.8; (*c* 0.5, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2953m, 1733s (C=O), 1513m, 1365m; δ_H (600 MHz; $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.032 (3H, s, $SiCH_3$), 0.55-0.62 (6H, dq, *J* 7.6, 4.8, 2.8, $Si(CH_2CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.96 (9H, t, *J* 7.9, $Si(CH_2CH_3)_3$), 1.05 (3H, d, *J* 6.9, 3'-CH_3), 1.17 (1H, dd, *J* 12.9, 11.5, 9-H_{ax}), 1.21 (3H, s, 10-CH_3), 1.28 (1H, d, *J* 14.2, 11-H_{ax}), 1.51 (1H, ddd, *J* 14.6, 12.1, 3.3, 3-H_{eq}), 1.55(1H, dd, *J* 15.2, 4.1, 5-H_{ax}), 1.63 (1H, ap. dt, *J* 13.3, 1.7, 9-H_{eq}), 1.69-1.74 (2H, m, 1''-H_A and 3-H_{ax}), 1.77 (1H, ap. dd, *J* 14.2, 1.4, 11-H_{eq}), 1.81-1.85 (1H, m, 1''-H_B) overlapping with 1.84 (1H, ap. dt, *J* 15.3, 2.0, 5-H_{eq}), 2.03 (3H, s, $COCH_3$), 2.10 (1H, dd, *J* 14.4, 6.3, 1'-H_A), 2.27-2.32 (2H, m, 1'-H_B and 3'-H), 3.37 (1H, dd, *J* 9.4, 7.8, 4'-H_A), 3.54 (1H, dt, *J* 8.6, 7.1, 2''-H_A), 3.62 (2H, m, 4'-H_B and 2''-H_B), 3.80 (3H, s, $ArOCH_3$), 4.09 (1H, dddd, *J* 16.6, 10.2, 4.0, 4.0, 2-H), 4.17 (1H, m, 8-H), 4.38-4.44 (2H, ap. q, *J* 11.4, OCH_2Ar), 4.81 (1H, s, 2'-CH_AH_B), 4.91 (1H, s, 2'-CH_AH_B), 5.02 (1H, m, 4-H), 6.87 (2H, d, *J* 8.6, Ar-meta-H), 7.25 (2H, d, *J* 9.4, Ar-ortho-H); δ_C (150 MHz; $CDCl_3$) -5.41 ($SiCH_3$), -5.4 ($SiCH_3$), 6.9 ($Si(CH_2CH_3)_3$), 7.2 ($Si(CH_2CH_3)_3$), 16.5 (3'-CH_3), 18.3 ($SiC(CH_3)_3$), 21.5 ($COCH_3$), 25.9 ($SiC(CH_3)_3$), 32.2 (10-CH_3), 34.3 (3-C), 35.6 (1''-C), 38.6 (5-C), 41.7 (3'-C), 41.9 (1'-C), 44.8 (9-C), 47.7 (11-C), 55.2 ($ArOCH_3$), 61.9 (2-C), 64.5 (8-C), 67.0 (2''-C), 67.5 (4-C), 67.6 (4'-C), 70.5 (10-C), 72.6 (OCH_2Ar), 96.7 (6-C), 111.1 (2'-CH_2), 113.7 (Ar-*meta*-C), 129.2 (Ar-*ortho*-C), 130.8 (Ar-*ipso*-C), 148.6 (2'-C), 159.1 (Ar-*para*-C) and 170.1 ($COCH_3$); Found (+ESI): $(MNa)^+$ 757.4518. $C_{40}H_{70}O_8Si_2Na$ requires 757.4507.

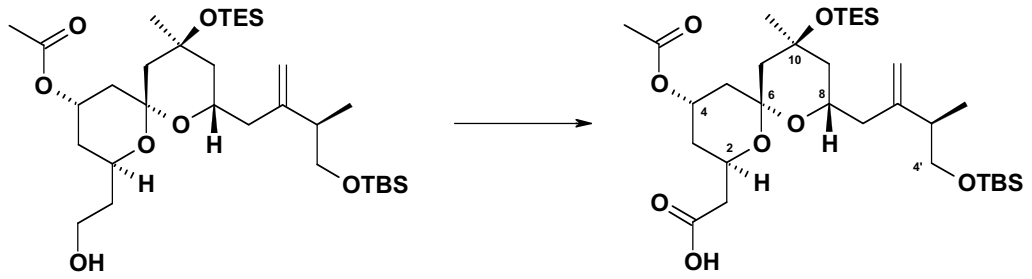
(2*S*,4*S*,6*R*,8*S*,10*S*,3'*R*) Acetic acid 8-[4'-(*tert*-butyldimethylsilanoxy)-3'-methyl-2'-methylenebutyl]-2-(2''-hydroxyethyl)-10-methyl-10-triethylsilanyloxy-1,7-dioxa-spiro[5.5]undec-4-yl ester



23

To a rapidly stirring mixture of acetate **23** (436 mg, 0.59 mmol) in CH_2Cl_2 (20 mL) and pH 7.0 buffer solution (1 mL) was added DDQ (269 mg, 1.18 mmol). After 1 h the reaction was quenched with saturated $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:2 then 1:1) afforded the title compound as a colourless oil (310 mg, 85%); R_f (Et_2O:petrol, 1:1) 0.31; $[\alpha]_D^{25}$ -57.4; (*c* 1.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3520br (OH), 2952s, 1735s (C=O), 1369m; δ_H (600 MHz; $CDCl_3$) 0.05 (3H, s, $SiCH_3$), 0.054 (3H, s, $SiCH_3$), 0.56-0.63 (6H, dq, *J* 7.9, 7.6, $Si(CH_2CH_3)_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.94 (9H, t, *J* 7.9, $Si(CH_2CH_3)_3$), 1.08 (3H, d, *J* 6.7, 3'-CH_3), 1.16-1.24 (4H, m, 10-CH_3 and 9-H_{ax}), 1.30 (1H, d, *J* 14.3, 11-H_{ax}), 1.57 (1H, dd, *J* 15.0, 4.0, 5-H_{ax}), 1.60-1.68 (4H, m, 3-H_{ax}, 3-H_{eq}, 9-H_{eq} and 1''-H_A), 1.73-1.76 (1H, m, 1''-H_B) overlapping with 1.78 (1H, ap. dd, *J* 14.2, 1.2, 11-H_{eq}), 1.87 (1H, ap. d, *J* 15.0, 5-H_{eq}), 2.03 (3H, s, $COCH_3$), 2.11 (1H, dd, *J* 13.8, 6.6, 1'-H_A), 2.32 (1H, m, 1'-H_B), 2.40 (1H, m, 3'-H), 2.83 (1H, bs, OH), 3.36 (1H, dd, *J* 9.1, 1.4, 4'-H_A), 3.64 (1H, dd, *J* 9.7, 4.7, 4'-H_B), 3.70 (1H, m, 2''-H_A), 3.84 (1H, m, 2''-H_B), 4.10-4.14 (1H, m, (probable dddd), 8-H), 4.21-4.25 (1H, m (probable dddd) 2-H), 4.80 (1H, s, 2'-CH_A), 4.91 (1H, s, 2'-CH_B), 5.04 (1H, m, 4-H); δ_C (150 MHz; $CDCl_3$) -5.4 $(SiCH_3)_2$, 6.7 ($Si(CH_2CH_3)_3$), 7.2 ($Si(CH_2CH_3)_3$), 17.0 (3'-CH_3), 18.3 ($SiC(CH_3)_3$), 21.5 ($COCH_3$), 25.8 ($SiC(CH_3)_3$), 32.2 (10-CH_3), 34.1 (3-C), 37.3 (1''-C), 38.5 (5-C), 41.3 (3'-C), 43.0 (1'-C), 44.6 (9-C), 48.0 (11-C), 59.6 (2''-C), 63.0 (2-C), 64.4 (8-C), 67.3 (4-C), 67.9 (4'-C), 70.6 (10-C), 96.8 (6-C), 111.2 (2'-CH_2), 148.8 (2'-C), 170.9 ($COCH_3$); Found (+ESI): $(MNa)^+$ 637.3943. $C_{32}H_{62}O_7Si_2Na$ requires 637.3932.

(2*S*,4*S*,6*R*,8*S*,10*S*,3'*R*)-{4-Acetoxy-8-[4'-(*tert*-butyldimethylsilanyloxy)-3'-methyl-2'-methylene-butyl]-10-methyl-10-triethylsilanyloxy-1,7-dioxa-spiro[5.5]undec-2-yl}acetic acid (24)

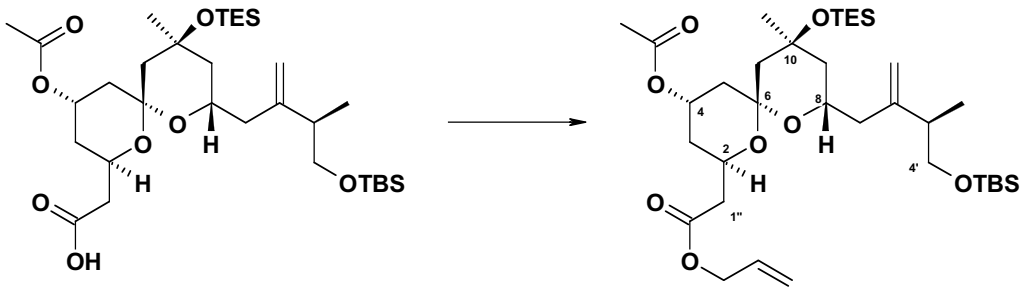


24

To a solution of alcohol (305 mg, 0.49 mmol) in CH_2Cl_2 (20 mL) and 1.0 M solution of pyridine/CH_2Cl_2 (5 mL) at rt was added Dess-Martin periodinane (420 mg, 0.99 mmol). A further portion of Dess-Martin periodinane (420 mg) was added after 3 h. The reaction was quenched after a further 2 h with a 1:1 solution of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ (30 mL) then extracted with a 1:1 mix of EtOAc:Et_2O (3 x 50 mL). The combined organic extracts were washed successively with saturated $NaHCO_3$ (30 mL), saturated brine (30 mL) dried ($MgSO_4$) and concentrated *in vacuo.* Flash column chromatography eluting with Et_2O:petrol (1:3) afforded intermediate aldehyde (288 mg, 98%) as a yellow oil. This was dissolved in 0.6 M solution of $NaClO_2$ in pH 7.0 buffer solution (8 mL) and 2-methyl-2-butene (3.5 mL, 2.0 M solution) was added and the resultant solution was stirred at rt for 2 h. After this time starting material still visible by TLC so a further portion of 0.6 M $NaClO_2$/ buffer solution (8 mL) was added followed by 2-methyl-2-butene (3.5 mL). The reaction was quenched after a further 3 h by the addition of saturated NH_4Cl solution (30 mL) and extracted with EtOAc (3 x 50 mL) then CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* Flash column chromatography eluting with Et_2O:petrol (1:1) afforded the title compound as a colourless oil (220 mg, 70% 2 steps, 75% from aldehyde); R_f (Et_2O:petrol, 1:1) 0.35; ν_{max} (thin film)/cm^{-1} 2924s, 1736s (C=O), 1714s (C=O), 1370m; δ_H (600 MHz; $CDCl_3$) 0.06 (6H, s, $(SiCH_3)_2$), 0.59 (6H, q, *J* 7.9,

Si(CH_2CH_3)$_3$), 0.90 (9H, s, SiC(CH_3)$_3$), 0.94 (9H, t, *J* 7.9, Si(CH_2CH_3)$_3$), 1.07 (3H, d, *J* 6.9, 3'-CH_3), 1.25 (3H, s, 10-CH_3), 1.29 (1H, ap. d, *J* 16.3, 9-H_{ax}), 1.35 (1H, d, *J* 14.3, 11-H_{ax}), 1.51-1.63 (2H, m, 5-H_{ax} and 3-H_{eq}), 1.69 (1H, ap. d, *J* 13.5, 3-H_{ax}), 1.78 (1H, d, *J* 14.3, 11-H_{eq}), 1.81 (1H, dd, *J* 16.1, 1.6, 9-H_{eq}), 1.97 (1H, ap. d, *J* 15.1, 5-H_{eq}), 2.05 (3H, s, $COCH_3$), 2.12 (1H, dd, *J* 14.0, 6.5, 1'-H_A), 2.32 (2H, ap.dd, *J* 13.8, 6.5, 1'-H_B and 3'-H), 2.51 (1H, dd, *J* 15.9, 6.7, 1''-H_A), 2.58 (1H, dd, *J* 15.9, 4.3, 1''-H_B), 3.38 (1H, dd, *J* 9.5, 8.1, 4'-H_A), 3.61 (1H, dd, *J* 9.8, 5.1, 4'-H_B), 4.18 (1H, m, 8-H), 4.44 (1H, m, 2-H), 4.84 (1H, s, 2'-CH_A), 4.91 (1H, s, 2'-CH_B), 5.05 (1H, m, 4-H); Found (+ESI): $(MNa)^+$ 651.3748. $C_{32}H_{60}O_8Si_2Na$ requires 651.3724.

(2*S*,4*S*,6*R*,8*S*,10*S*,3'*R*)-{4-Acetoxy-8-[4'-(*tert*-butyldimethylsilanyloxy)-3'-methyl-2'-methylene-butyl]-10-methyl-10-triethylsilanyloxy-1,7-dioxa-spiro[5.5]undec-2-yl}-acetic acid allyl ester (25)

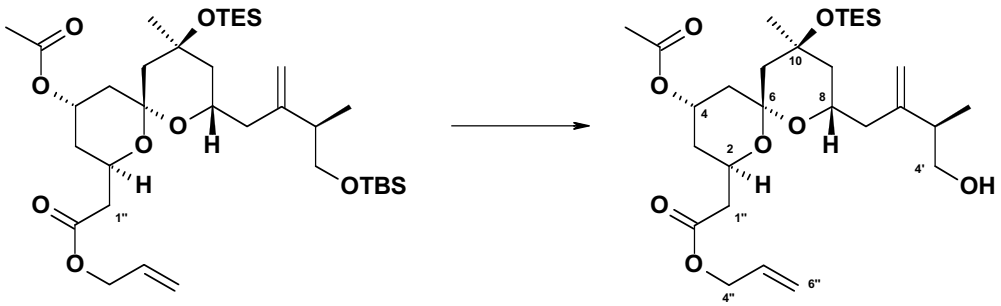


24 **25**

To a solution of acid (180 mg, 0.28 mmol) in THF (4 mL) at rt was added cesium carbonate (242 mg, 0.74 mmol) followed by allyl bromide (64 µls, 0.74 mmol) and reaction mixture was stirred overnight. The reaction was quenched with saturated NH_4Cl solution (20 mL) and extracted with Et_2O (4 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O:petrol (1:1) afforded the title compound as a colourless oil (183 mg, 82%); R_f (Et_2O:petrol, 1:1) 0.64; $[\alpha]_D^{25}$ -41.7; (*c* 0.75, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954s, 1736s (C=O), 1462m, 1369m; δ_H (600 MHz; $CDCl_3$) 0.032 (3H, s, $SiCH_3$), 0.036 (3H, s, $SiCH_3$), 0.56 (6H, q, *J* 7.9, Si(CH_2CH_3)$_3$), 0.90 (9H, s, SiC(CH_3)$_3$), 0.94 (9H, t, *J* 7.9,

Si(CH_2CH_3)$_3$), 1.07 (3H, d, *J* 6.9, 3'-CH_3), 1.19-1.22 (4H, m, 10-CH_3 and 9-H_{ax}), 1.28 (1H, d, *J* 8.2, 11-H_{ax}), 1.55-1.60 (3H, m, 3-H_{eq}, 5-H_{ax} and 9-H_{eq}), 1.75 (1H, dd, *J* 3.4, 8.4, 11-H_{eq}), 1.85 (2H, m, 3-H_{ax} and 5-H_{eq}) 2.04 (3H, s, $COCH_3$), 2.11 (1H, dd, *J* 5.1, 10.7 ,1'-H_A), 2.34 (2H, m, 1'-H_B and 3'-H), 2.41 (1H, dd, *J* 8.0, 15.4, 1"-H_A), 2.64 (1H, dd, *J* 5.4, 15.9, 1"-H_B), 3.39 (1H, dd, *J* 5.0, 9.5, 4'-H_A), 3.62 (1H, m, 4'-H_B), 4.22 (1H, m, (probable dddd), 8-H), 4.44 (1H, m, (probable dddd), 2-H), 4.58 (2H, d, *J* 5.7, 4"-H_A and 4"-H_B), 4.84 (1H, s, 2'-CH_A), 4.94 (1H, s, 2'-CH_B), 5.04 (1H, m, 4-H), 5.23 (1H, dd, *J* 10.6, 1.4, 6"-H_A), 5.30 (1H, dd, *J* 17.3, 1.4, 6"-H_B), 5.89 (1H, m, 5"-H); δ_C (150 MHz; $CDCl_3$) -5.42 ($SiCH_3$), -5.4 ($SiCH_3$), 6.8 (Si(*C*H_2CH_3)$_3$), 7.2 (Si(CH_2*C*H_3)$_3$), 16.4 (3'-*C*H_3), 18.3 (Si*C*(CH_3)$_3$), 21.5 (CO*C*H_3), 25.9 (SiC(*C*H_3)$_3$), 32.0 (10-CH_3), 33.9 (3-C), 38.4 (5-C), 40.3 (1"-C), 41.79 (3'-C), 41.81 (1'-C), 44.7 (9-C), 47.6 (11-C), 60.9 (2-C), 64.7 (8-C), 65.0 (2"-C), 67.0 (4-C), 67.7 (4'-C), 70.3 (10-C), 97.0 (6-C), 111.2 (2'-CH_3), 118.1 (4"-C), 132.2 (3"-C), 148.5 (2'-C), 170.4 (*C*O_2Allyl), 170.9 (*C*OCH_3); Found (+ESI): $(MNa)^+$ 691.4038. $C_{35}H_{64}O_8Si_2Na$ requires 691.4037.

(2*S*,4*S*,6*R*,8*S*,10*S*,3'*R*)-[4-Acetoxy-8-(4'-hydroxy-3'-methyl-2'-methylene-butyl)-10-methyl-10-triethylsilanyloxy-1,7-dioxa-spiro[5.5]undec-2-yl]-acetic acid allyl ester (26)

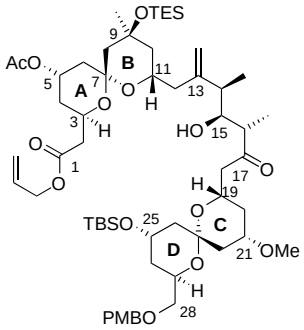


25 **26**

To a stirring solution of starting allyl ester **25** (28 mg, 0.03 mmol) in THF (0.5 mL) at 0 ^oC was added 8%HF-pyridine/10%pyridine/THF solution (0.2 mL). After 1 h a further aliquot of HF-pyridine solution (0.2 mL) was added and the reaction was stirred for 2 h.

The reaction was quenched carefully with saturated $NaHCO_3$ solution (4 mL) and extracted with EtOAc (4 x 20 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Flash column chromatography eluting with Et_2O:petrol (1:1 then 3:1) afforded the title compound as a colourless oil (21 mg, 93%); R_f (Et_2O:petrol, 1:1) 0.15; $[\alpha]_D^{25}$ -87.2; (*c* 0.5, $CHCl_3$); ν_{max} (thin film)/ cm^{-1} 3515br (OH), 2953m, 2876m, 1733s (C=O), 1369m; δ_H (600 MHz; $CDCl_3$) 0.49-0.58 (6H, q, *J* 7.9, $Si(CH_2CH_3)_3$), 0.93 (9H, t, *J* 7.9, $Si(CH_2CH_3)_3$), 1.09 (3H, d, *J* 6.9, 3'-CH_3), 1.15-1.20 (4H, m, 10-CH_3 and 9-H_{ax}), 1.23-1.29 (1H, m, 11-H_{ax}), 1.51-1.59 (2H, m, 3-H_{eq} and 5-H_{ax}) 1.63 (1H, ap.d, *J* 13.1 9-H_{eq}), 1.74-1.77 (1H, ap. dd, *J* 14.2, 1.7, 11-H_{eq}) overlapping with 1.76-1.80 (1H, m, 3-H_{ax}), 1.87 (1H, ap.d, *J* 14.9, 5-H_{eq}), 2.01 (1H, bs, OH), 2.05 (3H, s, $COCH_3$), 2.14 (1H, dd, *J* 14.1, 6.2, 1'-H_A), 2.33 (1H, dd, *J* 14.1, 6.6, 1'-H_B), 2.38 (1H, dd, *J* 16.4, 6.4, 1''-H_A), 2.50 (1H, m, 3'-H), 2.64 (1H, dd, *J* 16.4, 6.6, 1''-H_B), 3.47 (1H, m, 4'-H_A), 3.61 (1H, dd, *J* 9.9, 5.6, 4'-H_B), 4.27-4.31 (1H, dddd, *J* 12.0, 5.9, 5.9, 1.6, 8-H), 4.45-4.49 (1H, dddd, *J* 12,5, 6.0, 6.0, 1.9, 2-H), 4.52-4.60 (1H, dddd, *J*, 15.0, 12.4, 1.3, 1.3, 4''-H_A) overlapping with 4.53-4.62 (1H, dddd, *J*, 15.0, 12.4, 1.3, 1.3, 4''-H_B), 4.92 (1H, s, 2'-CH_AH_B), 5.05 (2H, s, 2'-CH_AH_B and 4-H), 5.24 (1H, dd, *J* 9.7, 1.1, 6''-H_A), 5.32 (1H, dd, *J* 15.9, 1.3, 6''-H_B), 5.90 (1H, dddd, *J* 16.0, 9.7, 5.3, 5.3, 5''-H); δ_C (150 MHz; $CDCl_3$) 6.7 ($Si(CH_2CH_3)_3$), 7.2 ($Si(CH_2CH_3)_3$), 16.5 (3'-CH_3), 21.4 ($COCH_3$), 32.0 (10-CH_3), 34.0 (3-C), 38.4 (5-C), 40.3 (1''-C), 41.7 (1'-C), 42.3 (3'-C), 44.8 (9-C), 47.6 (11-C), 60.9 (2-C), 64.9 (8-C), 65.2 (2''-C), 66.2 (4'-C), 67.0 (4-C), 70.3 (10-C), 97.0 (6-C), 112.2 (2'-CH_3), 118.3 (4''-C), 132.0 (3''-C), 148.2 (2'-C), 170.8 (CO_2Allyl), 170.9 ($COCH_3$); Found (+ESI): $(MNa)^+$ 577.3195. $C_{29}H_{50}O_8SiNa$ requires 577.3173.

Synthesis of **28**.



28

Dess-Martin periodinane (35 mg, 0.082 mmol, 1.5 eq.) was added in one portion to a solution of alcohol **21** (30 mg, 0.054 mmol) and pyridine (0.025 ml) in dichloromethane (2 ml) and the mixture was stirred for 1 h. A mixture of saturated sodium hydrogen carbonate solution and saturated sodium thiosulfate solution (1 ml, 1:1) was added to the reaction and stirred for 30 minutes. The mixture was extracted with diethyl ether (4 x 10 ml) and the combined organic extracts were washed with water and then saturated brine solution. Removal of the solvent under reduced pressure and purification of residue by rapid flash column chromatography on silica gel afforded *aldehyde* **4** that was used directly in the next reaction.

The *ketone* **5** (42 mg, 0.079 mmol) was dissolved in pentane (2 ml) and triethylamine (0.012 ml, 0.086 mmol) added before cooling the mixture to –78 ˚C. Dicyclohexylboron chloride (0.016 ml, 0.075 mmol, 0.95eq w.r.t. **5**) was added dropwise and the flask immediately warmed to 0 ˚C and stirred at this temperature for 1 h before re-cooling to –78 ˚C. Aldehyde **4** in pentane (1 ml plus 2x0.5 ml) was added and the reaction was stirred at –78 ˚C for 8 h. Methanol (0.5 ml) and pH 7 buffer (0.5 ml) was added to the reaction at –78 ˚C and then immediately warmed to 0 ˚C when hydrogen peroxide (0.5 ml, 30% v/v) and pH 7 buffer (1 ml)were added and the solution was stirred for 1 h. Addition of diethyl ether and extraction (3x10 ml) followed by washing the combined layers with of saturated sodium hydrogen carbonate solution ,water and brine. After removal of the solvent under reduced pressure then residue was purified by flash column

chromatography on silica gel (15% EtOAc in hexane to 40% EtOAc in hexane) to afford *aldol product* **28** (17mg, 44%).

δ_H (600 MHz; $CDCl_3$) 7.26-7.25 (2 H, m, J = 8.6 Hz, Ar-H), 6.87-6.85 2 H, m, J = 8.6 Hz, Ar-H), 5.92-5.88 (1 H, dddd, J = 17.2, 10.5, 5.7, 5.7 Hz, H_c), 5.32-5.30 (1 H, dddd, J = 17.2, 1.5, 1.5 Hz, H_B), 5.24-5.23 (1 H, app dd, J = 10.4, 1.3 Hz, H_A), 5.18 (1 H, br, $H_{13'}$), 5.05-5.04 (1 H, m, H_5), 4.94 (1 H, br, $H_{13'}$), 4.57-4.56 (2 H, m, $H_{D/D'}$), 4.51 (3 H, m, OCH_2Ar, H_{27}), 4.40-4.38 (1 H, m, H_3), 4.29-4.27 (1 H, m, H_{11}), 4.12-4.10 (1 H, quin, J = 3.9 Hz, H_{25}), 3.99-3.96 (1 H, m, H_{19}), 3.79 (3 H, s, $ArOCH_3$), 3.65-3.64 (1 H, ddd, J = 8.8, 3.1, 3.1 Hz, H_{15}), 3.50-3.46 (3 H, m, H_{21}, $H_{28/28'}$), 3.31 (3 H, s, $C_{21}OCH_3$), 2.95-2.91 (1 H, dd, J = 18.0, 4.1 Hz, H_{18}), 2.90-2.85 (1 H, dd, J = 18.0, 8.9 Hz, $H_{18'}$), 2.70-2.66 (1 H, dq, J = 8.8, 7.1 Hz, H_{16}), 2.63-2.60 (1 H, dd, J = 16.0, 5.7 Hz, H_2), 2.48-2.44 (1 H, dq, J = 7.0 Hz, H_{14}), 2.40-2.36 (1 H, dd, J = 16.1, 7.7 Hz, $H_{2'}$), 2.31-2.27 (1 H, dd, J = 14.6, 9.1 Hz, H_{12}), 2.25-2.22 (1 H, m, H_{20}), 2.17-2.14 (1 H, dd, J = 17.8, 5.2 Hz, H_{24}), 2.13-2.08 (1 H, dd, J = 14.9 , 4.1 Hz, H_{12}), 2.06-2.05 (4 H, m, C5-OCOC**H**$_3$), 1.86-1.82 (1 H, m, J = 15.0, 1.9 Hz, H_6), 1.81-1.78 (1 H, m, H_4), 1.77-1.75 (dd, J = 14.3, 2.0 Hz, H_8), 1.73-1.67 (1 H, ddd, J = 13.5, 11.4, 3.7 Hz, H_{26}), 1.58-1.50 (6 H, m, H_4, H_6, H_{10}, H_{22}, H_{24}, H_{26}), 1.37-1.35 (1 H, app t, J = 11.9 Hz, H_{22}), 1.30-1.23 (1 H, d, J = 14.1 Hz, H_8), 1.26-1.19 (4 H, m, H_{10}, C9-CH_3), 1.04-1.03 (3 H, d, J = 6.9 Hz, C14-CH_3), 1.01-1.00 (3 H, d, J = 7.0 Hz, C16-CH_3), 0.94-0.91 (9 H, t, J = 8.0 Hz, $SiCH_2CH_3$), 0.85 (9 H, s, $SiMe_2C(CH_3)_3$), 0.57-0.53 (3 H, q, J = 7.7 Hz, SiC**H**HCH_3), 0.56-0.52 (3 H, q, J = 8.1 Hz, SiCH**H**CH_3), 0.03 (3 H, s, $SiCH_3$Me(tBu)), 0.01 (3 H, s, SiMe CH_3 (tBu)); δ_C (150 MHz; $CDCl_3$) 212.9 (C-17), 170.9 (OCOMe), 170.2 (C-1), 159.1 (ArCOMe), 148.0 (C-13), 132.1 (Allyl CH), 130.6 (ArC), 129.2 (ArCH), 118.3 (Allyl CH_2) ,113.9 (C-13'), 113.9 (ArCH), 98.4 (C-23), 97.0 (C-7), 74.0 (C-21), 73.2 (C-15), 72.9 (C-28), 72.7 (OCH_2Ar), 70.3 (C-9), 66.8 (C-5), 66.4 (C-19), 65.1, 65.0 (O**C**$H_2CH=CH_2$), C-27), 64.4 (C-25), 64.2 (C-11), 60.9 (C-3) ,55.5 (OCH_3), 55.2 ($ArOCH_3$), 49.7 (C-18), 48.5 (C-16), 47.7 (C-8), 45.2 (C-10), 43.2 (C-22), 41.5 (C-12), 40.3 (C-2,C-14), 38.5 (C-6), 36.9 (C-20), 35.6 (C-24), 35.2 (C-26), 33.9 (C-4), 32.0 (C9-CH_3), 25.9 ($SiMe_2(C(CH_3)_3$), 21.5 ($OCOCH_3$) ,18.1 ($SiMe_2(CMe)_3$) ,13.0 (C14-CH_3), 11.0 (C16-CH_3), 7.2 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), -4.9 ($SiCH_3$Me(tBu)), -5.0

(SiMeCH$_3$(tBu)); Found (+ESI): $(MNa)^+$ 1111.6179 for $C_{58}H_{96}O_{15}Si_2Na$ requires 1111.6180.